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OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles

by

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

OCTOBER 1949

RECENT ADVANCES IN OUR KNOWLEDGE CONCERNING THE NEPHROTIC SYNDROME*

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BRADLEY AND TYSON[1] in an excellent review last year concluded that "The nephrotic syndrome can be profitably viewed as a discrete entity. As such it remains an unsolved riddle." The purpose of the talk today is to examine the recent advances in our knowledge concerning this entity and to evaluate the various therapeutic agents which have been recommended for it.

It is unnecessary to define the nephrotic syndrome to this audience but for purposes of clarification it might be useful to review briefly its characteristics. Generalized edema, hypoalbuminemia, and heavy proteinuria are its most noteworthy features. Hypercholesterolemia and

* Presented February 18, 1949 in the Friday Afternoon Lecture Series of The New York Academy of Medicine. From the Medical Services, Maimonides Hospital, and the Department of Medicine, Long Island College of Medicine. The normal human serum albumin used in these studies was prepared by the American National Red Cross from the blood of voluntary donors. This material has been supplied to investigators by the American Red Cross as part of its National Blood Program. The opinions and conclusions are those of the authors and do not necessarily reflect the policy of the National Blood Program.

lipidemia are usually present. The absence of hypertension, nitrogen retention and severe anemia are noteworthy in most instances. The syndrome in very young children is usually described as lipoid nephrosis.[2] In many instances, the most careful study of these children does not allow a positive declaration as to the exact nature of the renal lesion. Apparently characteristic clinical examples of lipoid nephrosis may eventually emerge as unmistakable cases of chronic glomerulonephritis.

In most adults the persistent edema of renal origin represents a phase in the course of chronic glomerulonephritis. The remainder of these cases occur in intercapillary glomerulosclerosis (Kimmelsteil-Wilson's disease), renal amyloidosis, lupus erythematosus disseminatus, and occasionally, during the course of syphilis and renal vein thrombosis. In the past year there have been two reports[3,4] of a self-limited nephrotic syndrome following the administration of trimethadione for epilepsy. The discussion today will be limited to facts concerning the nephrotic phase of chronic glomerulonephritis. However, under the subject of treatment, an evaluation will also be made of the effectiveness of certain agents in the control of edema of lipoid nephrosis.

Natural History of the Nephrotic Phase in Chronic Glomerulonephritis. Although the fully matured nephrotic syndrome is easily recognized, its more subtle forms are frequently undiagnosed. This has led to a considerable disparity in reports of its incidence. In a study with Bloom,[5] it was found that evidence indicative of the nephrotic phase was present in the case histories of only 54 per cent of 50 consecutive patients dead of chronic glomerulonephritis at the Presbyterian Hospital in New York. Another 20 per cent may have had it. This left, however, 26 per cent in whom there was an absence of the criteria required for the diagnosis. Most individuals in this group were observed for periods of less than a year.

In a parallel study at the Goldwater Memorial Hospital, 10 of 11 patients with chronic glomerulonephritis observed over many years exhibited the classical findings of the nephrotic phase at some time during the course of the disease. This high incidence confirms the opinion of Baehr[6] and that of Christian.[7]

The onset and remission of the nephrotic phase is insidious and it is particularly difficult to assign a date for the initiation of the syndrome. It is, therefore, hazardous to present precise figures as to its duration. Nevertheless, Bloom and Seegal[5] ventured to suggest that the length

of the syndrome ranged from two months to five years. The average duration was 22.5 months.

The subclinical forms of the nephrotic state are only detected by the determination of the serum albumin and serum cholesterol values. A patient stigmatized by chronic glomerulonephritis may not be aware of the presence of slight edema; or the edema may be ascribed to a non-renal mechanism. If the serum albumin level is abnormally low it is good evidence for the presence of the nephrotic phase. Hypercholesterolemia is a confirmatory finding. Neither of these laboratory determinations should be interpreted out of context. It is presumed that the other causes of such abnormal values would be weighed. Caution should be exercised in depending upon total serum protein figures alone. It is possible that a coincident hyperglobulinemia may mask a depressed serum albumin to produce a net total serum protein value within almost normal limits.

The edema associated with severe dietary protein depletion or cardiac failure can usually be differentiated from that of the nephrotic phase. The former responds promptly to a highly nutritious regimen. The latter is evaluated in terms of the existing circulatory dynamics and the usual therapeutic aids.

When the edema is due to a combination of factors, physiological dissection is sometimes necessary to weigh the various forces. The following case report describes one aspect of this problem. The patient was a man of 36 with chronic glomerulonephritis of unknown duration. He was observed in the nephrotic state for a two year period. His serum albumin level was 3.1 gm. per cent. Edema was moderate. The patient left the hospital against advice and for the next month lived on a fluid diet consisting essentially of alcohol. He returned to the hospital in extremis with anasarca of the most flagrant type. His serum albumin value was 1.8 gm. per cent. He was immediately placed on a high protein diet and within the next month his serum albumin increased to 2.7 gm. per cent. The edema diminished coincidentally. In effect, the patient now clinically and chemically approximated his prebacchanalian state. Large amounts of dietary protein supplements did not further increase his serum albumin level nor decrease his edema. It is apparent, therefore, that the known edema producing factor of protein depletion has been separated from the unknown edema producing factor in the nephrotic syndrome.

The presence or the history of the occurrence of the nephrotic phase is a useful aid in the diagnosis of chronic glomerulonephritis. It serves to differentiate this disease from such other common causes of renal failure as pyelonephritis and arteriolar nephrosclerosis. In the study with Bloom[5] it was found that among 120 patients dead of renal failure there were no classical instances of the nephrotic phase in 50 patients with arteriolar nephrosclerosis or in 20 with pyelonephritis. Although edema occurred in about one-half of the patients in these two groups it was, in most instances, related to heart failure or severe malnutrition. Loeb[8] has stated that the nephrotic phase does not occur in arteriolar nephrosclerosis. Weiss and Parker,[9] and Fishberg[10] report the infrequency of generalized edema in pyelonephritis in the absence of heart failure. Mansfield, Mallory and Ellis[11] have again emphasized the absence of the nephrotic phase in a series of patients with arteriolar nephrosclerosis and pyelonephritis.

Neither the precise anatomical nor physiological changes in the kidney have been described to explain the development and the disappearance of the nephrotic phase. Nevertheless, it was of interest to determine the degree of tissue immunity induced during this state. The question of repetition of the nephrotic phase was therefore investigated. This may not be a valid question since many of the patients who emerge from the nephrotic phase enter a relatively short preuremic terminal stage. Irrespective of this consideration, the existence of the repetitive nephrotic phase has not been clearly established in our patient material. The few examples which have been described may very well represent fluctuations between the clinical and subclinical levels of the syndrome or edematous states due to more than one cause.

Some Physiological Considerations in the Nephrotic Syndrome. Starling's hypothesis[12] was stressed by Epstein[13] to explain the edema of the nephrotic syndrome. Starling postulated that the opposing action of the capillary blood pressure on the one hand and the plasma colloid osmotic pressure on the other largely controlled the flow of fluid into and out of the capillary vessels. Extracellular fluid distribution was thereby controlled. The oncotic pressure of the interstitial fluid and tissue tension were also factors in balancing the transcapillary pressures. Low tissue pressure and high distensibility of the skin govern the localization of edema fluid in areas such as the eyelids, genitals, and the

abdominal wall. Lange and his associates[14] applied a fluorescein technique to the study of capillary permeability in the nephrotic syndrome. They suggested that there was diffuse damage of the capillary membranes in this condition.

The appearance of edema in patients with the nephrotic syndrome is preceded by a long continued proteinuria attributable to a defective glomerular membrane. There is no evidence to suggest a significant excretion of protein by the tubules but reduced tubular protein reabsorption may be a factor. According to Addis[15] the proteinuria in glomerulonephritis is too small to account for the depletion of plasma and body proteins if synthesis continues at its usual rate of 55 gm. per day as described by Co Tui and his associates.[16] Addis hypothesizes that there is either a deficiency in this synthesis, for which there is no good evidence, or that proteins filtered through the glomerules run into a "digestive" block when absorbed through the tubules. Oliver[17] has presented experimental evidence which indicates that the metabolic processes of protein absorption in the proximal convoluted tubules may be disturbed. Addis has therefore suggested that "Perhaps failure of intracellular digestion is responsible for the accumulation of protein in the proximal tubule."

Whatever the mechanism for protein loss through the kidneys, there is a reduced serum albumin level with a concomitantly reduced colloid osmotic pressure. This is generally conceded to be a prime factor in the production of edema through a disturbance in the transcapillary balance of forces. However, the occurrence of spontaneous diuresis and loss of edema in the absence of any detectable change in plasma protein concentration is difficult to explain on this basis alone. There is no reliable evidence to suggest that the formation of abnormal proteins plays a role in the formation of edema.

In addition to hypoalbuminemia, there is probably sodium, chloride and water retention due to an imbalance between glomerular filtration and tubular reabsorption. Luetscher,[18] in studying the effect of intravenous salt-poor normal human serum albumin on nephrotic edema, found only a slight rise in serum protein concentration while glomerular filtration increased and the proportion of sodium reabsorbed diminished. He concluded that the reabsorption of an excessive proportion of sodium by the renal tubule is responsible for the edema of nephrosis and is of greater importance than the depressed serum albumin level.

Fox and McCune[19] have stressed another phase of electrolyte imbalance which they feel might explain the diuresis which occurred in the face of a depressed, unchanged plasma protein content, as noted by Loeb and his group.[20] They describe instances of low plasma sodium levels and low urinary sodium excretions in patients in the nephrotic syndrome. They suggest that intracellular edema may result from this reduced plasma sodium and cause disturbed function of organs such as the kidney. They recommend the oral administration of sodium lactate and sodium and potassium acetate in doses adjusted to maintain a urinary output of 140 m.eq./L of sodium and 100 m.eq./L of potassium. It is sometimes necessary to give 30 to 50 grams of these salts daily to raise the concentrations to the optimal levels. Thereafter, a maintenance dose of 5-15 gm. of each salt is required each day. With these agents they attempt to raise the concentration of sodium in the extracellular fluid and the concentration of bicarbonate in both the extra- and intracellular fluid. Thereby, they anticipate that fluid will move out of the cells, increase plasma volume, encourage increased renal sodium excretion and thereby produce diuresis. Fox and McCune[19] suggest, furthermore, that these alkaline electrolytes in tubular urine may inhibit the precipitation of protein in the renal tubules.[21] The authors report that all fourteen patients in the nephrotic state had a diuresis on this regimen.

Robinson and Farr[22] demonstrated the presence of an antidiuretic substance in the urine of three patients with nephrosis in the edematous phase and found it absent in two when they became edema free. The role of this substance in the pathogenesis of the edema must await further evaluation.

Treatment of the Nephrotic Phase. The major portion of the lifetime of the patient with chronic glomerulonephritis is symptom free. In point of fact, the presence of the disease is often only recognized by a chance urinalysis. Disability occurs during two periods: in the nephrotic state and in uremia. In the latter, the patient is usually free of edema of renal origin.

The discussion today is limited to a critique of the various suggested regimens or agents which are said to influence favorably the most distressing aspect of the nephrotic phase—edema. Before embarking on this stormy and wet journey, it might be profitable to consider with you the possibility of the effective control of glomerulonephritis. For, if nephritis could be prevented or if its earliest stages could be con-

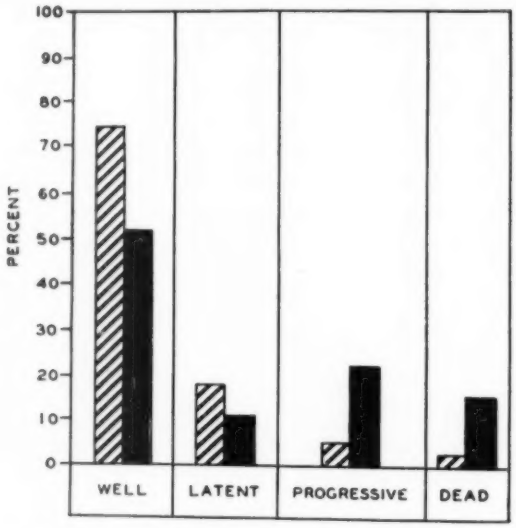
trolled favorably, in all likelihood the nephrotic phase would not develop.

The present notion is that most cases of acute glomerulonephritis follow a hemolytic streptococcus infection. A small proportion of this group progress to the chronic state. However, many patients with subclinical acute nephritis are not seen by a physician and members of this group, who do not heal, finally appear with chronic glomerulonephritis without a history of an acute attack. Longcope[23] believes that there are two types of glomerular nephritis: the one, the typical acute hemorrhagic Bright's disease with good prognosis and the other, a form characterized by insidious onset, persistent edema, and poor prognosis. It cannot be denied, however, that some if not all of the members of this latter group may represent the unrecognized subclinical examples of acute glomerulonephritis which have gone on to the chronic state.

Although the evidence is good to incriminate the hemolytic streptococcus as the instigant of acute glomerulonephritis, it is difficult to marshal convincing data that the maintenance of the prolonged course of chronic nephritis is dependent upon the persistence of hemolytic streptococcus infection. Exhaustive bacteriological and immunological studies[24] during long stages of this form of the disease have failed to yield evidence that a known biological agent was continuously active.

With the advent of the antimicrobial drugs, Williams, Longcope and Janeway[25] studied the effectiveness of sulfanilamide in 42 patients with acute glomerulonephritis. They gave a total of 2.4 to 3.6 gm. of the drug in six doses in each 24 hour period. The patients received a total of 6 to 169 gm. (av. 49 gm.). The sulfanilamide was administered over a period of 3 to 63 days (av. 17 days). The authors compared the course of the disease in these 42 individuals treated with sulfanilamide with that of a group of 108 similar individuals seen in the presulfanilamide days (Graph 1). They believe that the data allows them to conclude that "in the subjects receiving sulfanilamide the foci of infection have cleared up more rapidly, the signs of renal damage have disappeared more rapidly, the exacerbations of the nephritis following tonsillectomy have occurred less frequently, the duration of the edema and hypertension has been shorter, and the clinical recoveries have been greater.

"In the group of 42 patients treated with sulfanilamide there was one death in the acute stage. Complete recovery occurred in 15 of 33



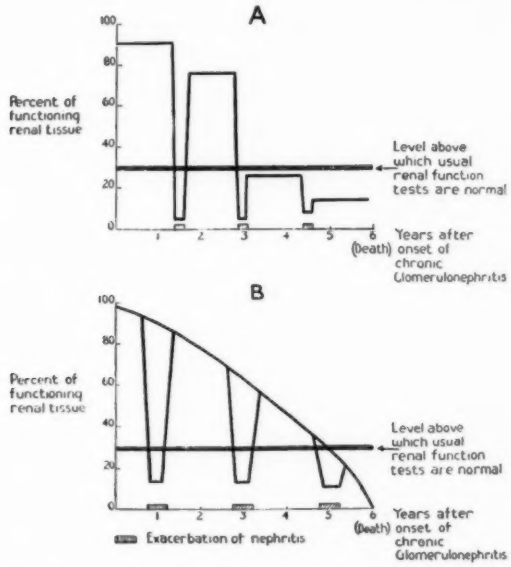
Graph 1.—Clinical outcome of patients followed for 2 years or longer. Comparison of the clinical outcome of 42 patients with acute glomerulonephritis (cross-hatch bar) treated with sulfanilamide, and 108 patients with acute glomerulonephritis (solid bar) observed in the pre-sulfonamide era. (Williams, R. H., Longcope, W. T. and Janeway, C. H. Am. J. M. Sc., 1942, 203:157.)

cases who returned for observation after 6 months and in 29 of the 39 patients, or in 74.3 per cent of those followed for at least 2 years. Three additional cases who have been followed for only a few weeks are in a quiescent stage. Five of the 39 patients are in the quiescent state, and 2 are in a progressive stage.

"In the control group of 108 patients, on the other hand, there were 12 deaths in the acute stage and 5 deaths following a progression to chronic nephritis. Of the entire group of 108 patients there are only 56 complete recoveries, giving a percentage of 52; 11 patients are in the quiescent stage and 24 in the chronic progressive stage of the disease.

"The course of the immunologic reactions as exemplified by the antistreptolysin titer of the blood stream has been practically the same in both groups. There was no evidence that sulfanilamide caused renal damage in any case."

This report has not led to general acceptance of the principle of



Graph 2—Schematic Description (*A and B*) Showing Two Possible Effects of Exacerbation on Mass of Functioning Renal Tissue in Hypothetical Patient with Chronic Glomerulonephritis. (Seegal, D., Lyttle, J. D., Loeb, E. N., Jost, E. L. and Davis, G. J. Clin. Investigation, 1940, 19:569.)

antimicrobial therapy throughout the course of acute glomerulonephritis. There is little doubt, however, that appropriate chemotherapy is justified in any stage of nephritis when the invading organism causes significant infection. During the nephrotic phase a variety of infections are prone to occur. These are usually amenable to the chemotherapeutic agents now available but the life-saving usefulness of these agents is not to be construed as affecting the natural history of the underlying disease.

There is inadequate evidence to relate precisely the persistence of the chronic stages of nephritis with infection. Two possible forms of pathogenesis[26] are schematically shown in Graph 2. In hypothetical form A, each successive infection exciting an exacerbation in a patient with chronic glomerulonephritis might produce fresh parenchymal damage and decreased renal reserve. This is the prevailing thought with regard to the pathogenesis of rheumatic fever where it is believed that repetition of the bouts of the disease produce the additive damage

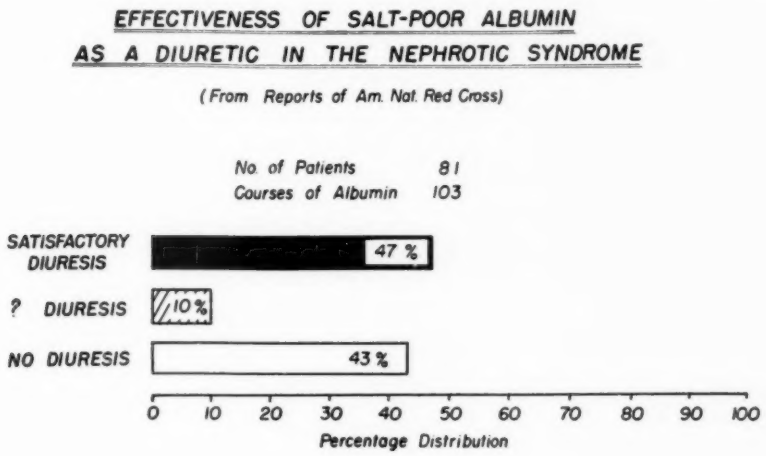
leading to cardiac failure. If this same pattern exists in chronic glomerulonephritis, one might be justified in placing individuals with this disease on a suitable chemoprophylactic regimen to minimize hemolytic streptococcus infection and its effects on the kidney. However, some of our patients who have had frequent exacerbations of nephritis have experienced a rather benign course. In contrast, other patients, who appeared to be unusually free of hemolytic streptococcus infection and exacerbations over a series of years, have progressed to the uremic stage.

The observations of Masugi,[27] Smadel[28,29,30] and many others have shown conclusively that the pathologic and clinical counterpart of human chronic glomerulonephritis may be produced in animals by the single injection of a specific antikidney serum. Recently Cavelti[31] has presented evidence that autoantibodies to kidney may play a role in glomerulonephritis.

If this analogy can be carried over to man, the scheme shown in hypothetical form B may be discussed. Here the initial nephritis is followed by a progressive decrease in renal function. The course and slope of the disease may have been established at the onset. The effect of the exacerbation may be dramatic but not necessarily effective in influencing the course. The correct answer may lie in a combination of these two possibilities.

If form B represents the mechanism for progression in human glomerulonephritis, obviously prolonged chemotherapy would be unjustified. Instead, a method for blocking a specific antigen-antibody reaction would have to be developed. With respect to this point Lange and his associates[32] have recently described data which lead them to conclude that glomerulonephritis is caused by a continuous organ-specific antigen-antibody reaction.

The Patient and His Edema. The most distressing symptom of the nephrotic phase is the edema. It may persist for 5 years, its average duration being in the neighborhood of 2 years. There are no means available at the moment which will guarantee that all patients in the nephrotic phase will be relieved of all their dropsy. It often becomes necessary for the patient to learn to live with some edema. Very often the patient is less concerned about his swelling than he is with the strict prohibitions presented to him concerning his diet. The methods now available to the physician to assist the patient in this state will now be considered.



Graph 3

Effectiveness of Salt (NaCl) Restriction in the Nephrotic Syndrome. Widal and Javel[33] in 1904 found that salt restriction in normal individuals led to a diuresis and weight loss. They furthermore noted that when these same individuals were placed on a high salt diet they gained weight, which was presumed to be fluid. A salt (NaCl) restricted diet for patients with edema is in common use today. The chief dissenting opinion is that of Fox and McCune[19] who, as stated earlier, have presented data which lead them to conclude that the edema of the nephrotic syndrome is dispelled more efficiently by the ingestion of sodium lactate and potassium acetate than by a salt-poor regimen. Fox and McCune report a complete diuresis in 14 patients who underwent this treatment. Acceptance of this form of therapy must await experience with the method in other clinics.

Certain of the diets now being advocated for the alleviation of edema may owe their efficacy to their low sodium content. The usual diet for a patient with the nephrotic syndrome limits the salt intake to one to two grams per day. The Kempner[34] rice diet contains 0.2 gm. of sodium and 0.15 gm. of chloride. On these low salt regimens the majority of patients may learn to live a reasonably normal life with a minimal amount of edema. The exact amount of salt in their diet

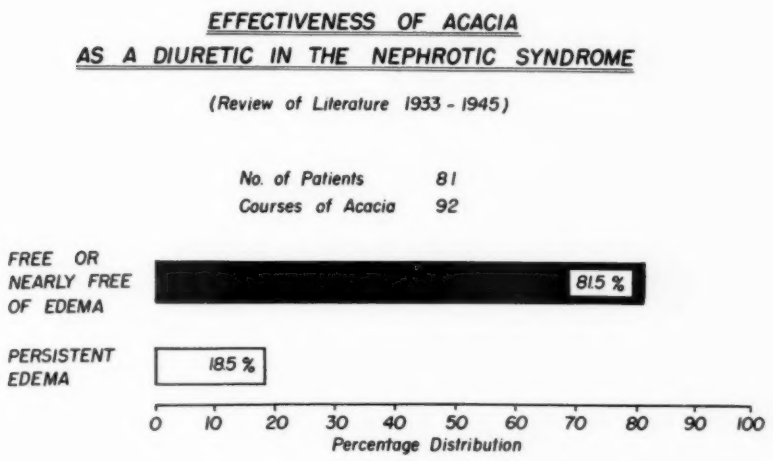
may be calibrated to give them optimal gustatory satisfaction with little incapacity due to dropsy.

Effectiveness of Salt-Poor Normal Human Serum Albumin as a Diuretic in the Nephrotic Syndrome. When human plasma and human serum albumin became available through the American National Red Cross Blood Collection Program, high hopes were entertained that the intravenous administration of salt poor normal human serum albumin would be the long sought for agent to control effectively the edema of the nephrotic syndrome. On physiological grounds this seemed reasonable. Furthermore, human serum albumin, aside from its value as an oncotic agent had a great advantage over pooled human plasma. Although the incidence of homologous serum jaundice is 4 per cent following the injection of pooled human plasma, no case of homologous serum jaundice has yet been reported following the administration of human serum albumin.

The American National Red Cross, through its scientific advisory and technical groups, made available sufficient albumin for precise studies of the usefulness of this material in the nephrotic syndrome. It is now possible to draw certain conclusions from the data thus far accumulated. Graph 3 shows the observations obtained in 81 patients who received 103 courses of albumin under controlled conditions. Most of these patients received a daily dose of 7.5 to 100 grams of albumin. A satisfactory, albeit usually transient and incomplete, diuresis occurred in 47 per cent of the 103 courses. A questionable effect was observed in another 10 per cent. No significant diuresis was detected in the remaining 43 per cent of the courses.

The failure of the serum albumin to be a more effective diuretic agent is naturally disappointing. The data make it impossible to predict which type of patient will respond and which will not. The mechanism of the diuretic action when it occurred could not be explained to the complete satisfaction of the investigators. All agreed that most of the injected albumin appeared in the urine within 24 hours. There seemed to be some indication that a transient increase in the serum albumin level occurred and that there was an expansion of the plasma volume.

There seems to be little doubt that salt-poor human serum albumin is a more effective agent than untreated plasma or salt-containing albumin. In one unit containing 25 gm. of salt-poor human serum albumin there are only 1.6 gm. of NaCl.


EFFECTIVENESS OF ACACIA
AS A DIURETIC IN THE NEPHROTIC SYNDROME
(Review of Literature 1933 - 1945)
No. of Patients 81
Courses of Acacia 92
FREE OR NEARLY FREE OF EDEMA
81.5 %
PERSISTENT EDEMA
18.5 %
0 10 20 30 40 50 60 70 80 90 100
Percentage Distribution

Graph 4

We may conclude that salt-poor human serum albumin may be a useful diuretic agent. Unless the material is provided by the American National Red Cross or a similar agency the cost is prohibitive. The diuretic effect when produced is usually transitory. All investigators in this field agree that no evidence has appeared to indicate that the administration of salt-poor human serum albumin affects the natural course of the underlying disease. Some concern has been expressed that the injected albumin may injure the kidney but this question is still unanswered.

Effectiveness of Intravenous Administration of Gum Acacia as a Diuretic in the Nephrotic Syndrome. Considerable controversy has developed concerning the advisability of using gum acacia in the treatment of the edema of the nephrotic syndrome. Although some preliminary studies were carried out on the physiological effectiveness of gum acacia during the First World War, the initial reports on its usefulness in the treatment of the nephrotic phase did not appear until 1933.[35] We have reviewed the data in 12 papers[35-46] reported between 1933 and the present. Graph 4 shows the information obtained in 81 patients with edema of renal origin in whom 92 courses of acacia were administered. It is seen that in 83 per cent of the courses, a favor-

able diuretic response occurred. It is difficult to ascertain from the published reports how long the non-edematous state prevailed after the diuresis. In only one-sixth of the courses is there an absence of a diuretic effect. A favorable diuresis occurred twice as frequently following the acacia regimen as when salt-poor human serum albumin was the therapeutic agent. It is difficult to compare the patient material in both series but the impression is gained that it did not differ markedly.

Lehnhoff and Binger[44] recommend the following schedule of treatment with gum acacia. The standard intravenous dose is 500 cc. of 6 per cent acacia in 0.06 per cent sodium chloride solution. This dose of 30 gm. is either given on 3 successive days or on 3 alternate days so that a total of 90 gm. is administered. The serum level of gum acacia is determined one day after the last injection. If it is found that this level is greater than 2.0 gm. per cent, no additional acacia is given. If the serum level is less than 2.0 gm. per cent and the patient continues to have edema, acacia therapy is maintained at the previous rate until either the patient is edema free or a serum level of 2.0 gm. per cent is reached. The average patient receives a total of between 90 and 180 grams of acacia for the course.

Goudsmit, Binger and Power[45] noted that the patients who received acacia showed a diminution in the serum protein level averaging 22 per cent. This drop reflected an increased circulating plasma volume. The colloidal osmotic pressure of the serum was increased in 43 per cent, unchanged in 39 per cent, and decreased in 18 per cent of the 28 patients studied. The changes in colloid osmotic pressure appeared unrelated to the degree of effectiveness of the treatment. The authors suggest that the action of acacia may be effected by a renal factor, namely chloride diuresis.

It is difficult from the data to evaluate the usefulness of the various adjuvants which have been used with acacia. However, the diuretic effect of acacia does not preclude the similar effect of another agent.

The chief objections to the use of acacia have been the reports of its long persistence in the blood stream and its deposition in the liver. Recently Mannix[46] has described death in a child of 5 with the nephrotic phase of chronic glomerulonephritis to whom more than 200 gm. of acacia had been administered. Mannix believes that the death was related to the injection of acacia.

Dick, Warweg and Andersch[47] noted a marked lowering of serum

TABLE I—COMPARATIVE DIURETIC EFFECTS IN CHRONIC RENAL EDEMA OF CHILDREN

(*Based on data by Janeway et al* [*Tr. A. A. P. 1948*])

	I.V. Salt-Poor Albumin	*Induced Measles*
Urine Protein	Quantitative Excretion	Decreased Excretion
Serum Protein	Slight Rise	Significant Increase
Freedom from Edema	Transient	1-6 Months
Patients Improved	50-60%	{5 of 5 with Lipoid Nephrosis {3 of 7 with Nephrotic Syndrome

proteins and a large tender liver in each of four patients who received acacia. They did not believe that this fall in proteins was a simple dilution effect. Further studies by Andersch and Gibson[48] revealed that only small amounts of acacia injected into rabbits and dogs were excreted in the urine, while the livers of rabbits contained 50 per cent of the injected acacia and the livers of dogs 30 per cent. They also studied two nephrotic patients. One received a total of 72 gm. of acacia of which only 14.6 gm. were excreted in the urine. In the second patient, 43 per cent of the injected 46 gm. was found in the liver. Yuile and Knutti[49] injected dogs with one weekly dose of about 2 gm. of acacia per kilogram of body weight for a period of 15 to 22 weeks. These dogs received a total dose of acacia ranging from 327 gm. to 671 gm. They exhibited a drop in plasma protein of from 42 to 71 per cent and a drop in blood fibrinogen of from 58 to 79 per cent. This reduction in fibrinogen was out of proportion to and more marked than the plasma protein fall. The authors, therefore, suggest that liver damage had occurred. Smalley, Binger, Bollman and Power[50] in 1945 restudied the problem of acacia toxicity. In a period of 76 days, 3 dogs received 8, 22 and 26 times the amount of acacia usually given to patients. In these dogs large amounts of acacia were found in the liver, but there was no evidence of impaired hepatic function, as measured by the bromsulfalein retention test, and the prothrombin and fibrinogen determinations. In support of this group, Johnson and Newman[51] concluded that the reduction of blood proteins and hematocrit after acacia therapy, in 8 patients with the nephrotic syndrome, was primarily

the result of an increase in plasma volume. They found no evidence of inhibition of plasma protein formation.

The Diuretic Effect of Induced Measles on the Nephrotic State in Children. Janeway and his associates[52] were impressed by the diuresis which occurred in a nephrotic patient who contracted measles on one of their wards. Blumberg and Cassady[53] were also aware of this relationship. It was common knowledge that a similar diuresis followed many infections but Janeway believed that measles was a particularly effective agent. After careful selection of patients and explanation of risks, he inoculated children in the nephrotic syndrome "by the nasal instillation of throat washings, taken in broth from patients in the Koplik spot stage of measles, treated with several hundred units of penicillin, and stored at −70° C. No attempt was made to modify the measles, but full doses of penicillin, and sometimes sulfadiazine or streptomycin were given throughout the febrile stage of measles in order to prevent secondary bacterial infection."

Twelve children were treated over a three year period. All five patients with lipoid nephrosis diuresed but only 3 of 7 patients in the nephrotic phase of glomerulonephritis lost their edema. The diuresis when it occurred appeared from the last day of fever to 8 days later and was consummated within 3 to 5 days.

Table I illustrates the comparative diuretic effects of intravenous salt-poor human serum albumin and induced measles observed in children by Janeway. The striking difference concerns the proteinuria. Under the salt-poor human serum albumin regimen, most if not all of the injected material appears in the urine. In contrast, in induced measles there is a sharp drop in the degree of proteinuria. This precedes the diuresis by 2 or 3 days. In these patients there is a significant rise in colloid osmotic pressure and total serum protein concentration. This is not generally observed in the albumin treated individual. Furthermore, the diuretic effect in the latter is transient. In the patients with induced measles, remissions have persisted for 1 to 6 months. Although none of the group are cured or healed, "the first three patients (followed for 3 years) are edema free, but still have a little proteinuria."

Since the initial effect in induced measles is a sharp drop in proteinuria, Janeway and his associates were attracted to the notion that the kidney, rather than an extra-renal site, was the area of major disturbance in lipoid nephrosis.

Conclusions

A review of the more recent knowledge concerning the nephrotic syndrome permits the following conclusions:

1. The majority of patients in a prolonged course of chronic glomerulonephritis experience the nephrotic syndrome.

2. The subclinical forms of this state are often undetected. Serum albumin and cholesterol determinations assist in establishing its presence.

3. Although the onset and remission of the nephrotic syndrome are often insidious, it would seem that its duration may extend from 2 months to 5 years with an average of 2 years.

4. The repetition of the nephrotic phase could not be established in a long series of case reports.

5. Since the nephrotic phase does not appear during the course of pyelonephritis and arteriolar nephrosclerosis, its reported or actual presence is often a useful diagnostic feature in the determination of the nature of the kidney lesion in patients presenting themselves in renal failure.

6. The mechanism to explain the formation and disappearance of edema is not well understood.

7. The dietary restriction of sodium chloride remains the most useful agent to control the edema of renal origin. However, recent studies have indicated that diuresis may occur in the nephrotic phase following the oral administration of sodium lactate, sodium acetate, and potassium acetate. This observation requires further investigation.

8. The intravenous administration of salt-poor normal human serum albumin produces a satisfactory though temporary diuresis in about one-half of the patients in the nephrotic phase. The natural history of the disease appears to be uninfluenced by this regimen.

9. A review of the case reports indicates that gum acacia is an effective diuretic agent in the nephrotic phase. At least four-fifths of the individuals so treated have experienced a diuresis. The retention of acacia in the liver is a limiting factor to its general use. Some clinicians are opposed to its use because of its long retention in the body. Recently a death has been reported in a child of 5 following the administration of acacia.

10. Induced measles produced a prolonged diuresis in all 5 patients with lipoid nephrosis. A similar diuretic effect occurred in 3 of 7

individuals in the nephrotic phase of chronic glomerulonephritis.

11. A comparison of the effectiveness of intravenous salt-poor normal human serum albumin with induced measles led Janeway and his group to conclude that whereas albumin therapy caused a quantitative appearance of albumin in the urine, induced measles produced a sharp diminution of proteinuria before the diuresis. This finding led Janeway to place the site of the defect in lipoid nephrosis within the kidney.

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HYPERSPLENISM*

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It has been the usual experience in medicine, that as scientific knowledge about disease grows, the number of etiologic entities within any given clinical syndrome increases, with a corresponding expansion and diversity of specific therapy. Tonight, we shall be discussing the much rarer opposite phenomenon, viz., a mechanism, hypersplenism, which appears to be common to a wide range of clinically and etiologically separate syndromes, for all of which, nevertheless, one therapeutic procedure, splenectomy, is now advised. It seems not to depend upon whether the symptoms are chronic or acute, whether they reflect recurrent and prolonged invalidism, or present as a rapidly fulminating emergency, which may threaten the survival of the patient in a matter of hours,—the results of splenectomy are equally dramatic.

John H. King of Johns Hopkins, reporting in August 1914 on "Studies in the Pathology of the Spleen,"[1] which he had just completed with Eppinger in Vienna, observed that "many diseases of the blood are associated with striking changes in the morphology of the spleen. Often, indeed, the gross change in this organ is the dominating feature of the clinical picture . . . yet little progress has been made in the attempt to correlate changes in the spleen with clinical symptoms. That this organ has important functions can hardly be questioned. There is, for example, considerable evidence to show that the spleen may have a marked influence on hemolysis. It is but a step then to assume that there may exist for the spleen conditions associated with an hyperactivity of some of its functions, let us say the function of influencing hemolysis. To such a condition the term "hypersplenism" may be applied . . . If it can be shown that important clinical symptoms consistently point to a hyperfunction of the spleen, and that these symptoms disappear, or are strikingly mitigated, when the spleen is removed from

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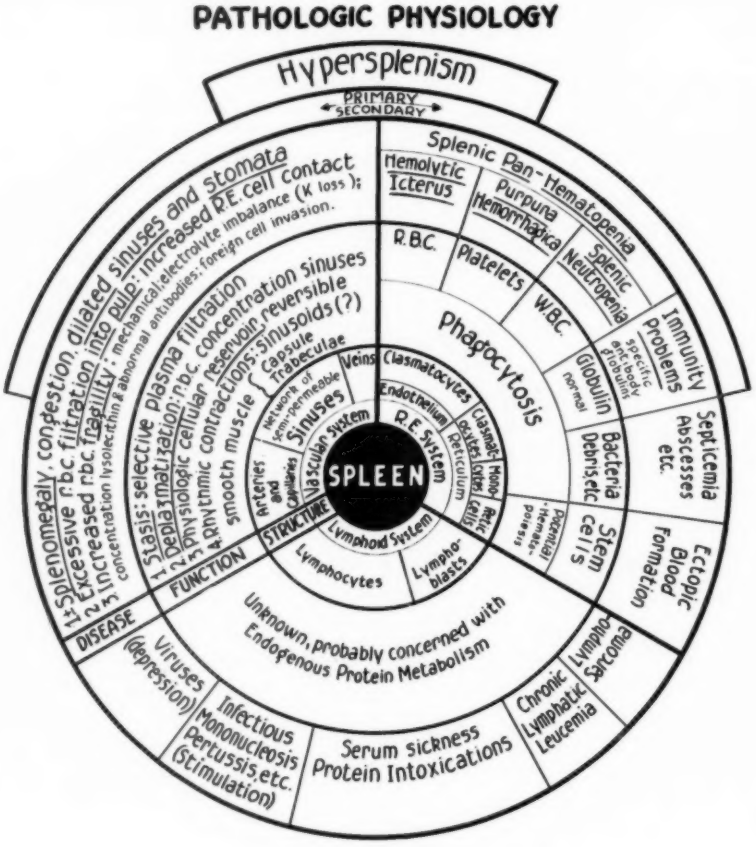

Figure 1—Pathologic physiology of the spleen

the body, an important step will have been taken toward defining the changes in function of the spleen." This is the first use of the term "hypersplenism," which we have found in the medical literature. A clearer forecast or a surer prophecy of the hypersplenic states which have since been recognized, and of their therapeutic response to splenectomy, could hardly be imagined.

The once enigmatic, physiologically non-essential spleen has now fully proved itself to be an exceedingly unstable, and, therefore, path-

ologically important organ. Whether it has inherited, as a Mendelian dominant gene factor, the *primary* capacity to withhold and destroy excessive numbers of circulating red blood cells (congenital hemolytic icterus),[2] or platelets (thrombocytopenic purpura),[3] or granulocytes (splenic neutropenia),[4] or destroys all three indiscriminately at the same time (pan-hematopenia),[5]—*or*, whether the spleen acquires these traits *secondarily*, through becoming involved in one or other of a number of unrelated constitutional diseases,[5]—when the hypersplenic mechanism has been established by the appropriate diagnostic procedures now clinically available, quick and sure action by the surgeon of the team is mandatory, and is usually effective.

As seen histologically, the spleen is not unique (Fig. 1), presenting simply a reduplication of the cellular elements common to many other tissues and organs in the body. The lymph follicles are identical with those found in all lymph nodes. The reticulo-endothelial phagocytes, though greater in quantity, are not unlike in quality those found in liver, bone marrow, mesenteric lymph nodes, and the diffuse connective tissues. No specific secreting cells which would appear to be potentially capable of producing an internal secretion have ever been described. The specificity of the "thrombocytopen" of Trolland and Lee,[6] and of splenin I and II of Ungar[7] has as yet been difficult of confirmation in other laboratories, including our own. The experimental extirpation of the spleen in many animal species, and the accumulated experience of emergency splenectomy for traumatic rupture of the normal human spleen,[8,9] have effectively confirmed these morphological findings and interpretations, and have firmly established the fact that this organ is not essential to the maintenance of normal health and longevity at any age in any species.

The Spleen and its Vascular Sinuses

We must turn then to anatomical considerations for at least a part of the explanation of the unique relationship which this organ seems to bear to the human pathological states, with which we are concerned. Unlike lymph nodes and liver, the spleen possesses a smooth-muscle-reinforced capsule and penetrating intra-parenchymal trabeculae, which provide an intrinsic mechanism for the rhythmic physiologic contraction and relaxation of this organ. A sharp contraction of the spleen occurs after voluntary muscular exercise, after hemorrhage and after

psychic (adrenalin) stimulation.[10] The diagnostician may take advantage of this neuro-muscular mechanism to obtain a non-surgical "biopsy" of the potentially mobilizable splenic cell content at any desired moment by securing peripheral blood cell and blood volume studies before and after the injection of adrenalin.[11] A biphasic curve of total cell and differential fluctuations will reflect within 60 to 90 minutes the initial contraction and subsequent compensatory hyper-relaxation of the spleen before it returns to its pre-adrenalin tonal equilibrium. By preceding such a study with sodium pentobarbital, it is possible to induce an initial relaxation of the muscular tone of the spleen with an increase in its sequestration of the blood elements reflected by a transitory reduction of as many as 37 per cent of the circulating erythrocyte population.[12]

This ability of the spleen to change its volume has been known for a long time, at least since 1723, when Stukeley[13] observed the spleen to enlarge in size as he injected blood into the jugular vein of dogs. The direct relationship, which has been repeatedly observed to exist between changes in spleen volume and circulating cell volume has inevitably focused attention sharply upon the nature and character of the circulation, which must govern this reservoir activity,—and as a direct corollary, the extent and effect of such storage on the involved blood cells. Increasingly ingenious methods have been developed for studying this most richly vascularized organ in the body. Proceeding from the older fixed tissue techniques, Knisely[14] perfected the procedures for direct observation by transillumination of the living intact spleen in a number of animal species, and concluded, contrary to Mollier[15] and Mall,[16] et al, that the circulation everywhere within the splenic pathway is closed. Large intercommunicating sinuses, with afferent and efferent physiologic sphincters, connect arterioles and veins, permitting periodic closure when distended with blood, in which phase the plasma passes through the sinus wall by filtration, leaving the red cells concentrated and completely shut off from the active circulation for as long as 10 hours at a time. MacKenzie, Whipple and Wintersteiner,[17] however, in attempting to repeat Knisely's observations on the spleen in the living animal, failed to confirm his interpretations. They believe the chief concentration of erythrocytes is in the splenic pulp rather than in the sinuses, the parenchyma receiving its complement of red cells through fenestrations in the club-like ampulae of Malpighi at

the ends of the capillaries. The red cells appeared to be slowed down or "blocked" from time to time by aggregations of white corpuscles, which subsequently gave way to permit re-entry of the erythrocytes through openings in the walls of the veins, synchronous with and mediated by the rhythmic contractions of the spleen which occurred as originally described by Barcroft.

During the spring of 1947, Sven Erik Björkman published a very complete monograph on the Splenic Circulation[18] from Prof. Faraeus' laboratory at the University of Upsala. He critically analyzes the investigations of the past 100 years, adding his own experimental animal and human studies in an attempt to extend and clarify the earlier observations. Using gelatin to induce erythrocyte rouleaux formation, and saponin to produce less elastic spherocytes in rabbits, Björkman found that the pulp cords contained very few and the sinuses most of the red cells, whereas in the untreated controls there was a more equitable distribution between pulp and sinuses. He interpreted this to suggest that small changes in the size and shape of suspended particles, or aggregations of particles are important to their vascular filterability. By injecting intravenously starch granules measuring 1 to 5 *mu* in diameter, and identifying their intra-vs extra-vascular position, it was possible to further measure the approximate size of the suspected stomata under various conditions. Whereas under physiologic conditions 95 per cent of the starch granules 1 *mu* or less in diameter were found to have passed into the pulp cords, while 80 per cent of the granules 5 *mu* were still in the sinuses, after inducing an acute splenic tumor by experimental streptococcus infection or by intoxication with an hemolytic agent, only 50 per cent of the larger starch granules remained within the sinuses. An enlargement of the vascular stomata, under these pathologic circumstances, was hypothesized. Transferring his observations to selected human autopsy material, Björkman believes he has evidence to support the concept of an identical human splenic vascular mechanism, in which in acute splenic tumor in man there is sinus dilatation with an accelerated intercourse for both plasma and corpuscular elements between sinuses and pulp cords, via broadened and distended stomata. Conversely, in chronic cardiac decompensation and hepatic cirrhosis, Björkman describes a pathological modification of the splenic sinus wall structure, as reported earlier by Matsui,[19] with an increasing number of longitudinal anastomoses between the normally

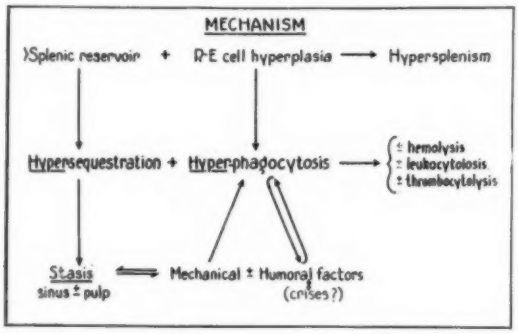

Figure 2—Mechanism of hypersplenic states, theoretical considerations.

annular fibrils in the sinus and venous walls, which would tend toward a compensatory preservation of the tightness of the sinus filter in resistance to a mounting portal hypertension.

Watzka[20] and Snook[21] have separated the various species in which the splenic circulation has been studied into two major groups: 1) those with poor sinus development, viz., cat, dog, cow, horse, sheep, swine, hedgehog, mole, ermine, weasel, and mice, and 2) those rich in these vascular structures: man, ape, rabbit, guinea pig, rat and squirrel. This variability in species and in pathologic splenic state may well explain the variations in emphasis in the study of an organ where it now seems certain that both sinuses and pulp cords are important circulatory reciprocals.

Thus it would seem fair to accept as our current working hypothesis (Fig. 2) the concept that the human spleen has a semi-open circulation, controlled by a filter mesh mechanism in the sinus wall, which by heredity or under many diverse pathologic conditions may be altered, either in the direction of greater or lesser selective permeability to the cellular elements of the blood. This circulatory mechanism, unique as compared with all other organs and tissues, operates to separate the cells from the plasma, and thus to concentrate in the spleen, both within and without the sinuses, in varying degree and quantity, blood cells of various types and quality.[22] The more disturbed the circulatory equilibrium, the more profound and prolonged the stasis, the more does the

spleen seem to lack discrimination and to withhold normal as well as fragile, senile and damaged elements.

The hypersplenic sequence of events my well include: abnormal stasis within splenic sinuses and/or pulp[23,24] calling for a compensatory increase in delivery of marrow elements; deplasmatization with increased mechanical intercellular friction;[25] loss of erythrocyte potassium with other electrolyte disequilibria, leading to increased fragility;[26] pathologic concentration of lysolecithin and lysolecithin-like, spherocyte-inducing biochemicals normally produced in physiological amounts by the R-E cells,[27] with hemolytic blocking[28,29]or other polyhemagglutinin antibodies[30] theoretically derivable from the R-E cells, exceptional opportunity for immediate contact-phagocytosis by R-E elements;—all in all an ideal environment for the establishment of a vicious cycle of cell withholding and cell destruction capable of acceleration or deceleration, depending upon a variety of factors. The dramatic immediacy of the termination of a true hemoclastic crisis at the operating table, at the moment of ligation of the splenic pedicle, strongly incriminates this inherent, chemico-mechanical splenic mechanism.[2]

The Role of the Bone Marrow

Turning now from the spleen per se, what role, if any, does the bone marrow play in the human hypersplenic states? The microcytic, spherocytic, hyper-fragility of the erythocytes associated with the hemolytic syndromes has been attributed to an inherited, inherent marrow defect.[31] Dameshek[32] and others have proved that all of these qualities are readily acquired by the definitive erythrocyte after marrow delivery, and it is difficult, if not impossible, to demonstrate these characteristics in the reticulocytes obtained directly from the marrow in these patients. The reports[33,34] of a normal survival time for transfused erythrocytes from normal donors in patients with acute hemolytic crises, in contradistinction to a relatively shorter survival time for their own marow product,—and that such transfusion support should be given routinely,—have not been confirmed in our experience. On the contrary, we believe the administration of borrowed red cells in acute hemolytic crises is both unnecessary (Fig. 3) and extremely dangerous. Attributing the excessive hemolysis of freshly transfused red blood cells in these patients to inaccurate isoagglutin or Rh typing, though this danger is always a possibility, can hardly account we believe, for

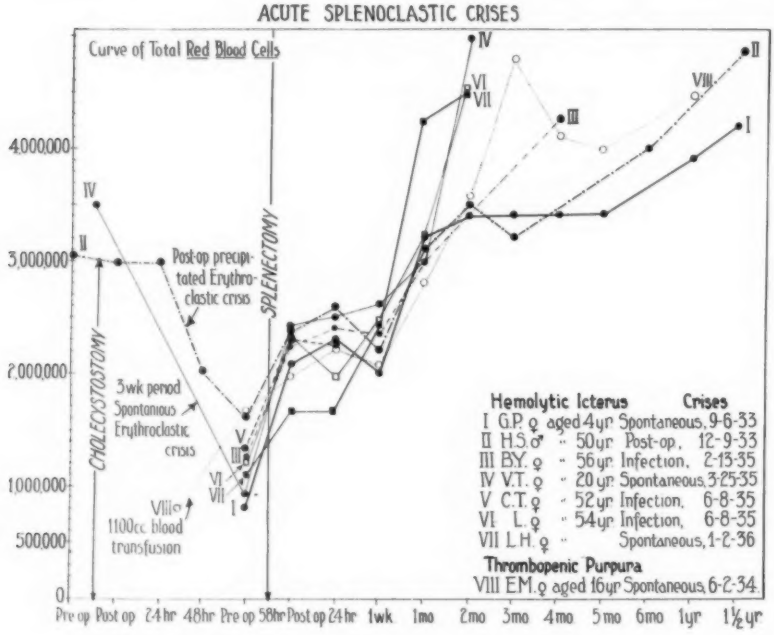
ACUTE SPLENOCLASTIC CRISES
Curve of Total Red Blood Cells
4,000,000
3,000,000
2,000,000
1,000,000
500,000
0
CHOLECYSTOSTOMY
SPLENECTOMY
Post-op precipitated Erythroclastic crisis
3wk period Spontanious Erythroclastic crisis
VIII 1100cc blood transfusion
Hemolytic Icterus Crises
I G.P. ♀ aged 4yr Spontaneous, 9-6-33
II H.S. ♂ " 50yr Post-op., 12-9-33
III B.Y. ♀ " 56yr Infection, 2-13-35
IV V.T. ♀ " 20yr Spontaneous, 3-25-35
V C.T. ♀ " 52yr Infection, 6-8-35
VI L. ♀ " 54yr Infection, 6-8-35
VII L.H. ♀ " Spontaneous, 1-2-36
Thrombopenic Purpura
VIII E.M. ♀ aged 16yr Spontaneous, 6-2-34
Pre op Post op 24hr 48hr Pre op 58hr Post op 24hr 1wk 1mo 2mo 3mo 4mo 5mo 6mo 1yr 1½yr

Figure 3—Three patients showing spontaneous erythroclastic crises, three with crises precipitated by infections, and one following surgery other than splenectomy, all responded similarly to emergency splenectomy irrespective of age or sex. The speed of red cell recovery was essentially identical in these patients with congenital hemolytic icterus and in patient VIII with a comparable anemia secondary to acute thrombocytopenic purpura.

all of the fatal reactions reported in the medical literature. Dameshek and Bloom[34] also find this phenomenon to vary from case to case. In Case 6 of their recently reported series, the red cell survival time, studied by the Ashby technique, was diminished during crisis, and became normal only after splenectomy. These authors have failed to find instances of sudden acute pan-marrow aplasia, as reported recently by Owren[35] in congenital hemolytic icterus, nor have we encountered this particular mechanism in the true acute hypersplenic crises, which have come under our observation in recent years. We have seen acute marrow aplasia, reflected by pancytopenia in the peripheral blood, but in each of these instances the differential diagnosis was established, first with reference to the exclusion of any hypersplenic factor, and then in terms

of the type of specific infection or chemical or drug idiosyncrasy, individually or collectively responsible. It is entirely possible for hypersplenism and marrow aplasia to occur coincidently in the same patient, or for aplasia to be precipitated in a patient with a previously demonstrated hypersplenic diathesis by any one of the many agents potentially operable in any other susceptible individual; but we believe the mechanisms should not, and need not, be confused. If, and when, epidemic disease does attack several members in a family with an inherited hyperinstability of the spleen, it may more readily invoke a sudden transitory hypersplenic episode, but any direct bone marrow damage is an additional complication adding greatly to the hazards, in contrast with the excellent prognosis when the hypersplenic mechanism alone is involved.

Two other more probable marrow mechanisms, which may be mediated by or through the pathologic spleen, have been seriously considered and proposed, viz., cell maturation arrest and/or delivery inhibition or "block." Krumbhaar[36] many years ago showed a sustained supra-normal rise in thrombocytes and erythrocytes in dogs post-splenectomy, suggesting some regulatory or inhibitory function affecting the level of circulating blood cells. Dameshek and associates have favored this interpretation of the cellular response which follows splenectomy in congenital hemolytic icterus, from studies of the fixed films and sections of marrow, and after finding "no evidence of erythrophagocytosis in studies of the splenic histology," also in fixed sections. Our own observations of fixed tissues in these cases have in every instance been supplemented by studies of the living marrow and spleen tissues, using supravital stains. Under these more favorable circumstances, it is quite easy to see, for example, in addition to those megakaryocytes rounded up in the "resting" phase, others in the same microscopic field with fragmenting cytoplasm in active platelet formation, even when a profound thrombocytopenia exists in the circulating blood. Likewise in aspirations or direct scrapings of living splenic tissue from any and all of the hypersplenic states, the highly phagocytic clasmatocytes or R-E cells are characteristically present in excessive numbers,—at times 10 to 12 per oil immersion field, from a spleen weighing perhaps 2000 grams,—differing only in the specificity of their phagocytized cell content, which in turn is directly related to the type and specificity of splenic reservoir cell sequestration, and is reciprocal to the circulating cytopenia. Specifically, in primary splenic neutropenia (Fig. 4), the bone

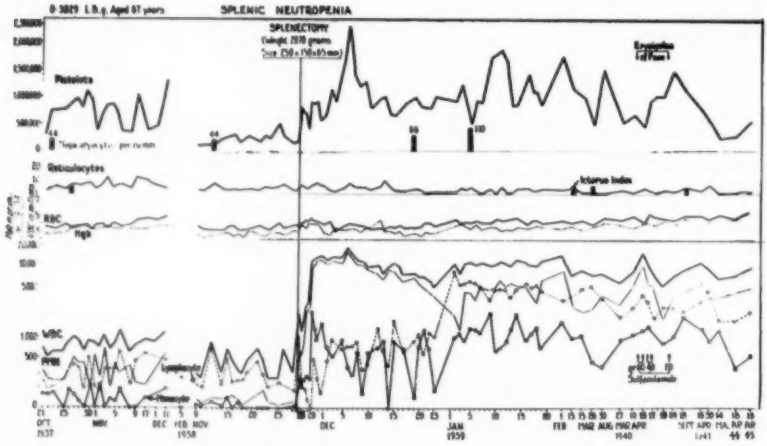

Figure 4—Primary splenic neutropenia progressing over a 12-month period to panhematopenia due to an extension of the same hypersplenic mechanism. Splenectomy completely and permanently restored the cellular and clinical equilibrium (11 years).

marrow is hyperplastic for neutrophilic myelocytes obviously maturing normally with delivery of motile band forms into the circulation at an accelerated rate; the sinuses and parenchyma in the greatly enlarged spleen have their usual complement of sequestered mature erythrocytes almost entirely replaced by these same granulocytes which may be found both without and specifically within the highly phagocytic R-E cells; the capillary circulation meantime may show as few as 25 granulocytes per cu. mm.; adrenalin contraction of the spleen may be expected to raise this circulating increment of granulocytes transitorially to 10,000 or more per cu. mm., in which case, splenectomy is almost certain to permanently correct the dyscrasia.

It will be clear from the foregoing discussion, that the bone marrow mechanism, which we have thought to be most frequently invoked in those pathologic states included in our definition of "hypersplenism," comprises the following interrelationships: maximum compensatory hyperplasia, with normal maturation and accelerated delivery of the specific marrow element or elements involved, which elements, nevertheless, remain in dangerously low negative balance in the circulating blood, due to an increasingly complete and absolute withdrawal of

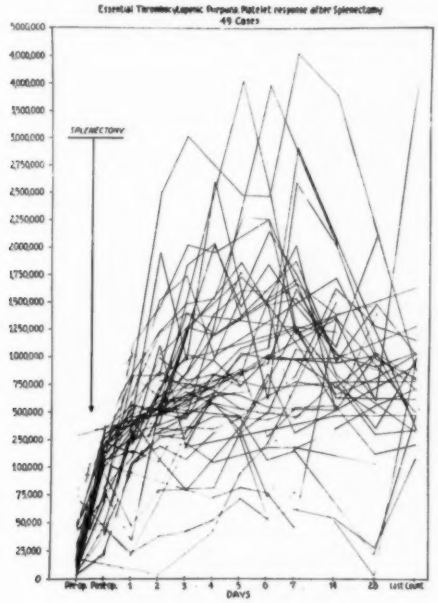

Figure 5—The peripheral thrombocyte response to splenectomy in 49 consecutive cases of thrombocytopenic purpura.

these essential blood cells by the spleen.

Final proof of the hyper-sequestration versus the marrow inhibitory role of the spleen in any given instance would seem to rest on the results of a carefully controlled study of the blood entering and leaving the spleen before and after adrenalin, during surgical exploration in an active phase of such cellular disequilibrium. During the past year we have been making such observations in appropriately selected patients with the surgical coöperation of Dr. Robert Zollinger. These data will be presented in detail elsewhere. Suffice it to say, here, that this direct evidence effectively eliminates any bone marrow inadequacy of cell maturation and delivery as major factors, at least in those patients so studied, at the same time placing the full pathologic responsibility on the splenic tissue in situ.

Reference to Fig. 5 on which are graphed 49 consecutive cases of primary splenic thrombocytopenic purpura, will reveal the immediacy,

the uniformity and the magnitude of the increase in circulating platelets which occurred at the operating table on the day of surgery, in all but five patients. Splenic artery and vein studies in a representative sampling of this series confirmed the bone marrow and adrenalin test interpretations of active platelet delivery, the splenic artery in one patient, for example, carrying 450,000 platelets per cu. mm. to the spleen, while the vein leaving the spleen contained only 17,000 platelets per cu. mm. Five minutes after adrenalin injection into the splenic artery, the splenic vein contained more than 400,000 platelets. This could be interpreted either as a closing of the sinus-pulp reservoirs temporarily by the contraction of the spleen creating an arterio-venous shunt, or it could represent a reservoir release of temporarily trapped platelets; in either interpretation the integrity and activity of the bone marrow is attested. In the five cases which showed a much slower and more gradual post-operative increase in the circulating platelets, the evidence might be interpreted as a gradual recovery of inhibited megakaryocytes reciprocal to the gradual elimination of some humoral agent produced by the spleen. Lacking as yet objective reproducible evidence of a circulating "thrombocytopen," this explanation must be left "sub judice" for the present.

In primary uncomplicated hypersplenism, then, as we have seen and interpreted these syndromes in our Clinic, the bone marrow plays only a reciprocal physiologic role, compensating, eventually maximally, in response to an excessive peripheral demand for blood cells, which demand fluctuates from time to time with the unpredictability of an inherently unstable and pathologicaly hyper-reactive spleen. The net increment of blood cells at any one moment in the circulating blood is always the resultant of the balance between supply and demand. Whenever any disturbance in this cellular equilibrium, so essential to health, occurs, either the supply must be increased or the demand reduced, promptly. In the hypersplenic states we must eliminate an excessive pathologic demand, more or less wholly created by the spleen, and which may or may not be compensable by the marrow. If and when the marrow becomes inadequate, the spleen must be promptly sacrificed, or the survival of the individual will be gravely threatened. Once freed of all splenic tissue, we have never found such individuals to show any further inadequacy or incompetence of the marrow for any and all demands through many years.

Primary Hypersplenism

Primary hypersplenism we define as an hyper-instability of the spleen, sometimes inherited as a Mendelian dominant gene factor, as in congenital hemolytic icterus, and, at other times, when direct human inheritance is difficult to establish, perhaps as a recessive character of infrequent expressivity. In such circumstances "spontaneous" hypersplenic episodes may occur, unrelated to any demonstrable internal or external environmental cause, such physiologic stresses as a normal pregnancy, and minor infections and traumata, frequently and repeatedly precipitate more or less severe hypersplenic exacerbations or "crises" in "susceptible" patients. For these reasons, whenever a true hypersplenism is recognized, prophylactic splenectomy must be seriously considered. Elective splenectomy is much to be preferred to emergency splenectomy for obvious reasons. Irrespective, however, of the degree of cytopenia or of the acuteness of the clinical syndrome, the response to splenectomy is equally prompt and sustained.[2]

Furthermore, it is seldom that we encounter a "pure" hemolytic or an unadulterated thrombocytopenic or neutropenic syndrome. The predominant clinical picture may be anemia, with or without jaundice, or purpura, or Ludwig's angina and infection, but any one of these symptom complexes will be found more often than not to have a subclinical if not clinical cytopenia involving one or more of the other elements of marrow origin. At different stages in the clinical course of the same patient, differing degrees of pan-hematocytopenia may be observed (Fig. 4) reflecting the variable withholding idiosyncracy of the pathologic spleen for the cells coming to it.

One of our patients, a 14 year old girl when first seen in consultation, had a history of more or less continuous, severe pan-hematocytopenia since birth. Every laboratory examination showed every organic function to be normal, except for a pan-marrow hyperplasia of normally maturing cells in normal relative proportions, and for the adrenalin test which was interpreted as reflecting an unequivocal splenic pan-cellular hypersequestration. Splenectomy was followed by a prompt peripheral hematologic re-equilibration, and by a complete clinical metamorphosis from chronic invalidism to normal health and physical activity. The surgery was consummated in October 1943. No other pathology has developed in the intervening 5½ years (Fig. 6).

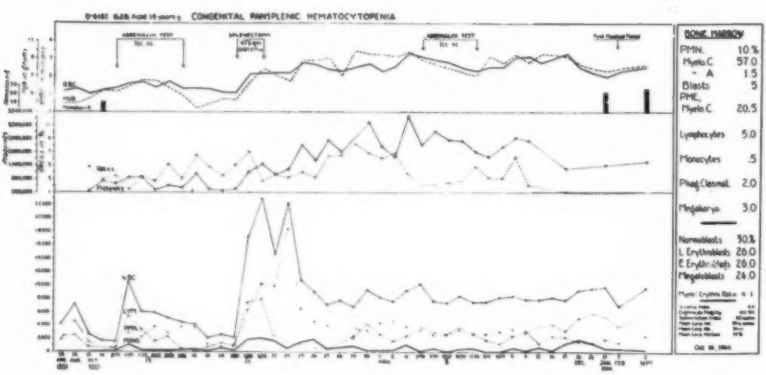

Figure 6—Congenital splenic panhematopenia from birth to 14 years; originally misdiagnosed as due to an hypoplastic bone marrow. Splenectomy has been followed by a sustained recovery clinically and hematologically.

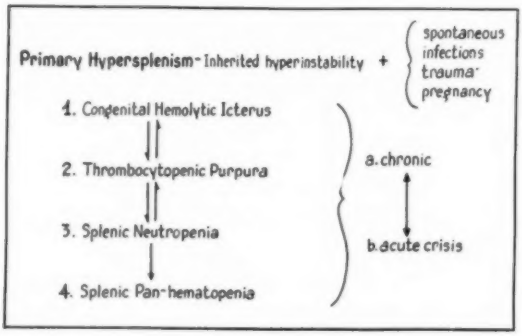

Figure 7—Primary hypersplenism.

Those clinical entities recognized under the general category of "primary hypersplenism" and their interrelationships as we have found them to occur in our series of case studies are shown in the graph (Fig. 7).

Hypersplenism Secondary to Other Diseases

During the course of a number of diseases the spleen may become secondarily involved (Table I). In a certain proportion of these cases

TABLE I—SECONDARY HYPERSPLENISM

Secondary or Acquired Hypersplenism—normal instability + { unusual / pathologic / stress }

Non specific—miscellaneous constitutional diseases.

1. Congestive
2. Infiltrative
3. Hemoblastic (the leukemias)
4. Inflammatory
5. Neoplastic
6. Myelofibrosis with splenomegaly, with or without hematopoiesis

TABLE II—326 SPLENECTOMIES
1932 - 1949

HYPERSPLENISM TOTAL	(82%) 270		
Primary		(65%)	176
Secondary		(35%)	94
MISCELLANEOUS TOTAL	(9.5%) 30		
Hypoplastic Anemia (relative splenic factor)			14
Polycythemia Rubra Vera			2
Sickle Cell Anemia			2
Lymphatic Leukemia			9
Myelogenous Leukemia			3
Erythroblastic Leukemia			1
NORMAL SPLEEN CONTROLS	(8.5%) 26		
Traumatic rupture (All Columbus Hospitals)			22
Secondary to other surgery (exposure)			4
TOTAL			326

there develops a syndrome identical with one or other of those already described as primary hypersplenism, in which both specific splenic hypersequestration and compensatory bone marrow hyperplasia may be demonstrated, though there is no familial history of such a trait. Hemoclastic crises may occur which threaten the survival of the individual quite independently of his basic disease. Under such circumstances splenectomy is indicated and may, and sometimes must, be undertaken,

TABLE III—270 HYPERSPLENIC CASES

1932 - 1949

270 SPLENECTOMIES FOR HYPERSPLENISM

PRIMARY

Congenital Hemolytic Icterus	75	Recurrences	
Thrombocytopenic Purpura	77	a. Accessory Spleens	4
Splenic Neutropenia	13	b. Generalized R.E. Cell Hyperphagocytosis	5
Splenic Pan Hematopenia	11		

SECONDARY

a. *Congestive Splenomegaly*		d. *Inflammatory Splenomegalies*	
Banti's Syndrome	42	Tuberculosis	3
Felty's Syndrome	6	Syphilis	1
Acquired Hemolytic Icterus	16	Moniliasis	1
b. *Infiltrative Splenomegaly*		Boeck's Sarcoid	2
Gaucher's Disease	4	Hodgkin's Syndrome	5
Xanthomatosis	1		
c. *Hemoblastic Splenomegaly*		e. *Neoplastic Splenomegaly*	
Lymphatic Leukemia	4	Retothelio Sarcoma	1
Myelogenous Leukemia	2	Hemangioma	2
Monocytic Leukemia	1	Multiple Myeloma	1

f. *Myelofibrosis* with fibrous splenomegaly without myeloid metaplasia 2

(With myeloid metaplasia 4 cases, no splenectomy)

with the more remote prognosis, however, correspondingly guarded. In no instance have we noted any exacerbation of the underlying disease process because of the splenic surgery, and most often the improvement which follows the re-establishment of a more nearly normal blood cell equilibrium is directly beneficial in the further management of the original disease.

In our series of 326 splenectomies (Table II), 82 per cent were diagnosed as hypersplenism, and of the 270 splenectomies for hypersplenism, 65 per cent have been classified as without otherwise demonstrable disease, therefore as primary, and 35 per cent as secondary to some other obvious basic pathology. Because of the frequency with which the spleen, when involved in other pathologic processes (Table III), has been observed to assume an aggressive activity against the blood cells entering its sinuses, it now seems appropriate to consider this

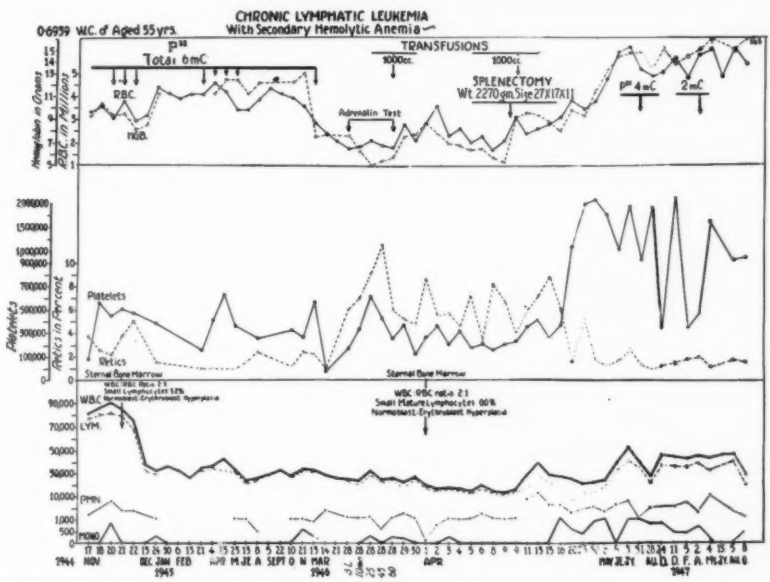

Figure 8—Acute erythroclastic crisis during the course of chronic lymphatic leukemia.

organ as possessing a considerable degree of "normal instability," not unlike, qualitatively, the inherited "abnormal hyperinstability" of the primary syndromes. The unique structure of this organ, as required for its physiologic functions (Fig. 1), lends itself admirably to circulatory disturbances associated with parenchymal cellular invasion, and the large complement of phagocytic cells already there await only the time and opportunity, which stasis and engorgement inevitably provide.

Three examples only will be cited from this series. During the course of chronic lymphatic leukemia (Fig. 8) in a white male, aged 57, who had been under satisfactory control with radioactive phosphorus for several years, there developed an acute hemolytic crisis. Appropriate laboratory studies ruled out both radiation damage and lymphocytic myelophthesia of the marrow as contributing factors while revealing a marked compensatory normoblastic hyperplasia, and splenic hyper-erythro-sequestration. Splenectomy was advised, after transfusions had proven ineffective, and was followed by an immediate cessation of

erythrocyte destruction. The underlying leukemia has continued to respond to small infrequent doses of radioactive P-32 to the present time. There have been no further hemolytic episodes.

A white male patient aged 39 years presented with all of the clinical and hematologic findings characteristic of acute primary thrombocytopenic purpura, including typical compensatory megakaryocytosis in the bone marrow without other demonstrable pathology. Splenectomy was followed by an immediate and sustained thrombocytosis, and the prompt disappearance of all purpuric manifestations. Histologic study of the spleen, however, revealed a well developed Hodgkin's granuloma, though neither liver nor lymph nodes, grossly or microscopically, showed any sign of this disease at this time. One year later the primary disease proved terminal, despite intensive therapy, but there was no recurrence of the purpura which had threatened survival from hemorrhage a year earlier.

A young woman, aged 20 years whose sister eight years previously had undergone splenectomy for Gaucher's disease, suddenly developed a rapidly enlarging abdominal tumor associated with profound peripheral blood changes. The total circulating leukocytes were only 1300 per cu. mm., the red cells 3,180,000, and the platelets 111,440. An adrenalin test decreased the tumor size and increased temporarily the circulating level of all of the normal blood elements. A sternal marrow study showed compensatory pan-marrow hyperplasia of all essential elements. An occasional Gaucher cell was found which served to establish the diagnosis. Similar studies of the sister's marrow revealed Gaucher cells in limited number, insufficient, however, to have influenced adversely the normal circulating blood cell equilibrium during the years since her earlier splenectomy. A 5000 gram spleen was removed without complications, followed immediately by the re-establishment of a normal sustained circulating level of all blood cells. Marriage and a normal pregnancy have been accomplished without untoward incident meantime.

Reference to Table III will show the range of diseases thus far encountered in our clinic, which have shown at some time during their clinical course, an involvement of the spleen sufficient to precipitate a more or less acute hypersplenic crisis, for which complication, surgery has been deemed imperative for survival. In none of these individuals have we been able by history or direct examination of blood relatives

to establish an hereditary factor. It is for this reason that we are hypothesizing a so-called "normal instability" of the spleen in its reservoir function for any or all of the blood cells, which due to the unique circulatory mechanism of this organ, plus its high content of R-E cell phagocytes, permits of ready imbalance in the circulating levels of the blood elements, which normally pass through or remain only temporarily in its parenchyma.

Acute Hemoclastic Crises

As already stated, the hypersplenic mechanism, whether primary or secondary, may precipitate some of the most acute critical acellular clinical syndromes which the physician and surgeon are called upon to diagnose and treat. Uncontrollable hemorrhage, a profound hemolytic anemia, or sudden sepsis may dominate the clinical picture. An immediate and thoroughly critical blood and bone marrow study is the first essential in the differential diagnosis. There may be insufficient time for a confirmatory adrenalin test or other extensive laboratory investigations. The theoretical considerations, which may explain this sudden negative balance between bone marrow supply and peripheral demand for any or all of the essential blood elements, we believe involve both the mechanical and/or humoral factors inherent in the vascular and cellular organization of the spleen (See Figs. 1 and 2). Whether the blood platelets, the erythrocytes, the granulocytes, or any possible combination of these elements are found to be deficient in the blood stream, the marrow must be hyperplastic for their precursors, without evidence of maturation arrest or qualitative abnormalities, if and when a true uncomplicated hypersplenism is the sole cause. In such syndromes, splenectomy is followed by a prompt and complete cellular re-equilibration, as reflected in the seven patients with acute erythroclastic crises in congenital hemolytic icterus and in the one patient with acute thrombocytopenic purpura (Fig 3). The curve of recovery of the red blood cells in each of these eight cases follows the same general pattern and timing, though the anemia in the first seven was hemolytic in origin and in the eighth it was secondary to hemorrhage. All of the factors which govern the specificity and degree of cellular deficit from patient to patient, and in the same patient from time to time are still unrevealed, but the evidence to date tends to incriminate the spleen rather than the bone marrow.

Relative Hypersplenism

In certain patients, who have experienced permanent marrow damage from industrial toxins, but in whom progressive mesenchymal destruction has been halted by removal from the environment, the normal physiologic reservoir function of the spleen may be sufficient to prevent cellular recompensation. After a sufficient period of supportive therapy, if the marrow hyperplasia continues to prove inadequate for the demand, splenectomy should be considered and will permit at times in selected patients, a more nearly normal circulating increment of cells.

Traumatic Rupture of the Spleen

Control studies have been made in those healthy individuals who have suffered sudden traumatic rupture of the spleen requiring emergency splenectomy for intra-abdominal hemorrhage and shock. In a survey of some 22 such individuals, the hematologic equilibria and the health and clinical resistance to ordinary infections have remained unimpaired (Table II). The normal human spleen is apparently not essential to life or health. Conversely the pathologic human spleen may threaten both health and longevity.

Post-Splenectomy Failures and Recurrences

The importance of differential diagnosis in the establishment of a true hypersplenic syndrome cannot be overemphasized. Obviously other mechanisms may simulate superficially these specific splenic entities, the most common of which involve the bone marrow, upon the integrity of which the body is dependent for its continuing resupply of new cells throughout life. Progressive marrow hypoplasia on the basis of any nutritional deficiency or toxic etiology, intrinsic or extrinsic in origin, must be recognized and corrected per se at the earliest possible moment. Myelofibrosis and osteopetrosis may be accompanied by compensating extramedullary hematopoietic splenomegaly, which when associated with a precipitated hypersplenic episode may strongly suggest splenectomy. Under such circumstances a positive adrenalin test will usually reflect a sharp increase in circulating nucleated red blood cells and myelocytes, but on occasion such evidence of local splenic hematopoiesis is lacking. If repeated bone marrow aspirations fail to reveal active blood cell regeneration from any and

all sites (sternum, spinous process, iliac crest, ribs), it may be necessary to aspirate the splenic parenchyma directly, or secure a tissue biopsy, before a judgment may be reached as to the relative importance of the productive versus the destructive roles of the spleen in any particular instance. In six such patients only two showed a predominant hyperdestructive activity by the enlarged spleen with negligible hematopoietic function. Both of these patients benefited by splenectomy. A tightly packed avascular leukemic marrow may simulate at times, an hypoplastic state, and with a sub-leukemic peripheral absolute leukopenia, anemia and thrombocytopenia, may lead to an erroneous interpretation of the splenomegaly.

In only a very few instances, fortunately, have we encountered a generalized R-E cell hyperplasia and hyperphagocytosis, in our non-bone marrow cytopenic states, so that liver, lymph nodes, marrow and connective tissues participated sufficiently to render clinically ineffective the removal of the excessively large increment of phagocytes in the spleen. Until proven otherwise, therefore, the principal pathologic focus in these patients may be assumed to be the spleen.

Accessory Spleens

An initial characteristic post-splenectomy remission may at times be followed after a few months or even after several years by a recurrence of the same or an entirely different type of hypersplenic syndrome. Experience has taught us to be immediately suspicious of some remaining accessory splenic tissue when this occurs. The marrow is again studied immediately and must show specific hyperplasia of the deficient circulating elements without maturation arrest or abnormal qualitative alterations. Accessory spleens or implanted splenotic fragments from a traumatically ruptured or surgically torn spleen may become hypertrophied and functionally pathologic. Re-exploration is definitely indicated when the laboratory data confirm a recurrent mechanism of hypersequestration and destruction. Thorotrast visualization will frequently assist the surgeon in locating the embryonic splenic rests in remote areas, including the retroperitoneal gutter.

Our first patient to be subjected to splenectomy during an acute erythroblastic crisis in congenital hemolytic jaundice experienced a dramatic recovery hematologically and clinically. which lasted 4½ years (Fig. 9). At the end of this period the same type of hemolytic,

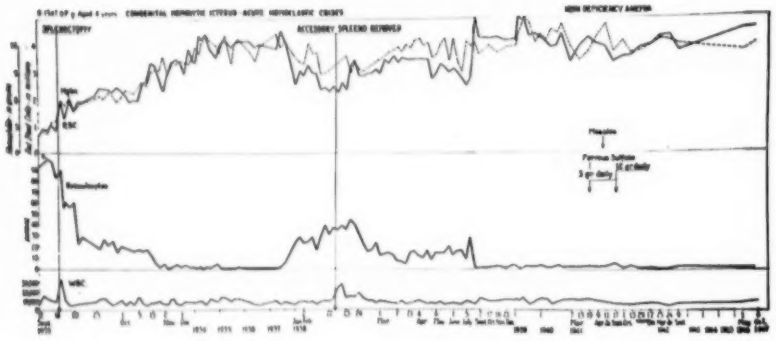

Figure 9—Recurrent hemolytic icterus caused by accessory splenic tissue. Recovery followed removal of 3 small accessory spleens.

icteric anemia re-appeared with reticulocytosis and compensatory normoblastic marrow hyperplasia identical with the first episode. When all medical measures had failed, a surgical re-exploration was undertaken and three small accessory spleens, totaling not over 5 gms. by weight in all, were found and removed. Mesenteric nodes and a biopsy of the liver were obtained at the same time from normal appearing tissues, and histologic examination confirmed the normalcy of these organs. The accessory splenic tissues, however, contained excessive numbers of highly phagocytic clasmatocytes loaded with red blood cells, and a second remission followed their removal. This has continued to the present time 11 years later,—16 years after the first operation.

The fact that few carefully studied hypersplenic episodes represent a pure single cell strain sequestration has been previously emphasized, together with the observation that the same individual patient may at different times show different cell-type deficits, reflected by entirely different clinical syndromes—all of which tends to center attention upon splenic tissue, its unique circulatory system, functionally designed for storing normal cells and salvaging damaged and senile blood elements,—rather than upon the organ of their origin, the bone marrow. This double danger of differential splenic selectivity was demonstrated in one of our patients in two dramatic episodes separated in time by 18 months. A young man 16 years of age (Fig.10) developed without previous warning, an acute erythroclastic crisis, typical of congenital

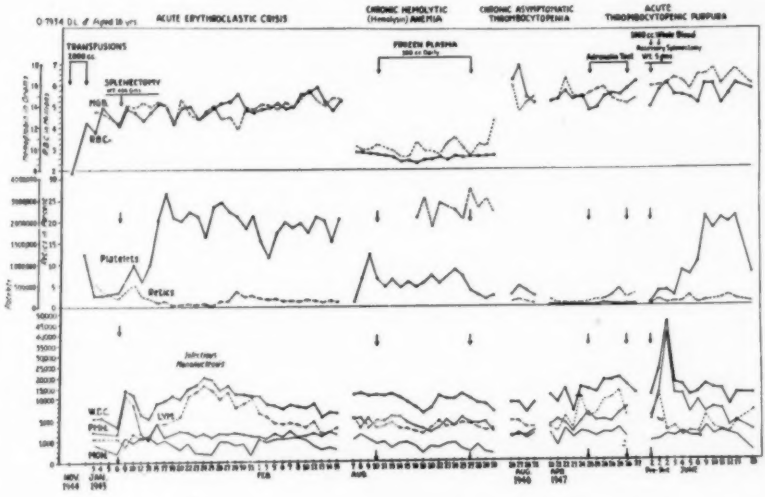

Figure 10—Primary congenital hemolytic icterus, acute crisis, relieved promptly by removal of the spleen. Eighteen months later an acute thrombocytopenic purpura without anemia was promptly relieved by the removal of an accessory 5 gm. spleen.

hemolytic jaundice. Complete recovery followed splenectomy. Some eighteen months later he developed, equally suddenly, an acute spontaneous fulminant thrombocytopenic purpura without any evidence of hemolytic anemia. Bone marrow studies confirmed the presence of increased numbers of actively multiplying and fragmenting megakaryocytes apparently responding to an increased peripheral demand for platelets. All other laboratory data excluded any other possible contributing mechanism. Following preoperative blood transfusions, a re-exploration was made and a 5 gram accessory spleen was discovered at the upper pole of the left kidney retroperitoneally. Upon its removal there was an immediate cessation of oozing in the operative field and the studies of the blood showed a coincident re-appearance of platelets in large numbers. There has been no further cellular disequilibrium in this lad to date.

Reference is made in this general connection to the patient already cited, who first presented with a relatively pure primary splenic neutropenia, only to develop within twelve months a splenic panhemato-

penia involving all of the circulating blood elements, with complete and permanent pan-cellular re-equilibration following splenectomy, continuing to date 11 years (Fig. 4).

Failure of complete and permanent restoration of health following splenectomy in true hypersplenic states will only be encountered in those individuals in whom the hypersplenism is secondary to progressive constitutional disease involving other organs. The ultimate outcome in such patients obviously will depend upon the effectiveness of the therapy for the primary disease. Nevertheless, when the predominant clinical syndrome in such patients can be proven to reflect an hypersplenic mechanism, this complication may and must be considered on its own merits. The best clinical judgment in our clinic has been more frequently than not to eliminate the focus of disease in the spleen together with the accompanying and resultant hypersplenic cellular imbalance, both of which threaten the health and survival of the patient. Only if a substantial cellular contribution is actually being made by a compensating, ectopic hematopoietic focus in the spleen, will the patient be less well off without rather than with his spleen.

Contraindications to Splenectomy

The contraindications to splenectomy may be sharply defined and clearly stated: 1) any acute or chronic bone marrow damage; 2) myelofibrosis, and 3) osteopetrosis in which the splenomegaly usually reflects ectopic hematopoiesis; 4) pan-myelophthesia; 5) ectopic splenic hematopoiesis plus secondary hypersplenism.

Summary and Conclusions

The spleen has inherited a unique anatomical structure, in which the relationship between smooth muscle capsule, pulp, and large fenestrated sinuses makes for an ideal physiologic reservoir for blood cell storage. The selective concentration of the stored elements of the blood, through the mechanism of deplasmatized stasis,—which in turn probably hastens unfavorable qualitative alterations in these cells,—when combined with an abundance of naturally occurring R-E cells, provide a basis for an apparent inherent homeostatic cellular instability in acquired, and an inherited hyper-instability in primary hypersplenism. A sub-acute, low-grade cellular disequilibrium may lead in one patient to chronic invalidism; in another, the same mechanism may result in a

vicious cycle, in which an acutely developing negative cellular balance will threaten survival. The resulting anemia, leukopenia or thrombocytopenia, which may be highly selective and specific, or in any combination and degree, underlie and govern the wide range of symptoms and signs which characterize these syndromes. Therefore, when the bone marrow is eliminated as a contributing factor, and a basic splenic mechanism is established, prompt removal of the spleen and all accessory splenic tissue provides the only assurance of a complete and lasting hematologic and clinical remission.

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NEWER ADVANCES IN GOUT*

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GOUT is an extensively studied, and yet obscure disease. It is of great interest to many branches of medicine: metabolism, arthritis, cardiovascular and renal disease, allergy, and orthopedics. The name of the disease is unusual in medical terminology. The term "gout" is derived from the Latin gutta, a drop. It was introduced in the thirteenth century to indicate that a noxa affected a joint by falling into it drop by drop. All students of the disease are fully aware that the term is somewhat naive, antiquated and has no nosological significance. Still, it is being commonly used because of its archaic-aristocratic dignity and because it is preferable to other terms, e.g., podagra, which only connotes "pain in the foot" and therefore should be reserved for and limited to this classic manifestation of gout. Another term "hereditary hyperuricemia" represents only one of the genetically transmitted chemical abnormalities of the disease. Since the exact etiology of gout is unknown the term gout probably will be retained until further progress in the knowledge of the disease will lead to a better and etiologic denomination.

HISTORY

The clinical manifestations of the disease were well known to Greek and Roman physicians. The writings of Aretaeus of Cappadocia, Caelius Aurelianus and Hippocrates contain excellent clinical observations on gout, e.g., Aretaeus observed that during a remission a gouty individual was capable of winning the Olympic games.

Strict differentiation of gout from other joint diseases was attempted by Sydenham[1]—who was himself afflicted with the disease for the major part of his life—in the classical "Tractatus de Podagra et Hydrope" (1683). The next century saw completely new aspects of the disease through discoveries in the field of chemistry. Scheele (1776) found uric acid to be a constituent of kidney stones[2] and twenty years later

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TABLE I—HISTORICAL REVIEW

Sydenham	1683	Differentiation of gout from other joint diseases
Scheele	1776	Identified uric acid in a kidney stone
Wollaston	1797	Discovered uric acid in tophi
Pearson	1798	Discovered uric acid in tophi
Garrod	1848	Discovered hyperuricemia—"Thread Test"
Miescher	1871	Nucleoproteins and nucleic acid in cell nuclei
Kossel	1879-1891	Purines are building stones of nucleic acid
Fischer, Emil	1907	Chemical structure of uric acid and purines
Folin	1913	Method for uric acid determination in blood
Blauch and Koch	1939	Method for determination of "true uric acid" with uricase

Wollaston (1797), and Pearson (1798) discovered the presence of uric acid in the tophi of individuals afflicted with gout.[3-4] It was almost exactly one hundred years ago that Garrod (1848) established hyperuricemia as a feature of gout.[5] With the famous "thread test" he discovered increased amounts of uric acid in the blood of gouty individuals. After Miescher (1871) had studied the role of nucleoproteins and nucleic acid in the cell nuclei[6] and Kossel (1870-1891) the role of purines as building stones of nucleic acid,[7] Emil Fischer (1907) established the chemical structure of uric acid and its relationship to that of purines.[8]

The important function of disturbed purine metabolism in gout was further elucidated by numerous clinical studies which were made possible by the introduction of reliable clinical methods for the estimation of uric acid concentration in the blood by Folin (1913)[9] and later by modifications by Benedict (1931)[10] and Folin (1934).[11] Although these methods did not specifically determine uric acid they were extremely helpful in metabolic studies of gout. The newer methods[12-14] avoid the inclusion of other substances giving the same color reaction as uric acid by employing specific enzymes, uricases, for the determination of "true uric acid."[15-18] Table I briefly summarizes the historical developments in gout.

In the following discussion only a few problems of gout will be presented: 1) Status of uric acid in the blood (uric acid partition), 2) hereditary hyperuricemia and its relation to disturbed lipid metabolism, 3) allergic factors in gout.

Status of Uric Acid in the Blood (Uric Acid Partition)

Garrod attributed gout to diminished elimination of uric acid by the diseased kidney.[5] There is, however, no evidence of renal disease or impaired kidney function in gouty individuals who have suffered several or even many acute attacks of gout, although in the late course of the disease renal damage, hypertension and azotemia may complicate the clinical picture. On the other hand, uric acid clearance of gouty individuals with high uric acid levels in the blood is lower than that found in individuals with hyperuricemia due to other diseases, e.g., leukemia. In normal subjects injection or ingestion of urate markedly enhances the clearance and results in rapid excretion of uric acid. In gouty subjects these processes are retarded and the recovery of administered uric acid is often not possible. The diminished elimination of uric acid might be caused by a specific impairment of renal mechanisms responsible for uric acid excretion. Especially in early cases of gout a specific renal defect of this sort is unlikely. All evidence points to retention of uric acid in the blood and in the tissues and possibly to an abnormally functioning fixation mechanism as a cause of the diminished elimination by the kidney. Impaired kidney function, present in later stages of the disease, is demonstrable with our proven kidney function tests and then represents a superimposed factor which causes with retention of various substances in the blood, additional retention of uric acid.

The problem of solubility of uric acid and urates in body fluids has been the subject of many studies. Uric acid is weak and dissolves in water in small amounts only. Sodium urate is more soluble[19] but its solubility is depressed by the addition of sodium chloride. A physiologic solution of sodium chloride dissolves only one tenth of the amount soluble in distilled water.[20] The solubility of sodium urate in body fluids is much higher, however, than the determination of its solubility in physiologic solution of sodium chloride would suggest. Sodium urate solutions are characterized by properties specific for colloidal solutions such as opalescence, gel formation and the Tyndall phenomenon.[21,22] This observation precipitated a discussion as to the existence of a colloidal form of uric acid in body fluids.[23,24]

Regardless of certain controversies about the colloidal state of uric acid, clinical observations years ago led to the assumption of "free" and

"bound" uric acid. It was Minkowski[25] who first postulated the existence of combined uric acid in blood. Benedict and his co-workers[26] succeeded in isolating a compound of one molecule of uric acid with one molecule of dextrorotatory ribose from the blood of various species of animals and from human blood. It was assumed that this substance derives either from inosinic acid by oxidation of the hypoxanthine component or from guanylic acid by oxidation of the guanine moiety. This is the only organic combination of uric acid in the animal body the existence of which has been definitely proved.[27]

A few French authors attempted to differentiate free uric acid from combined uric acid.[28-30] Chabanier, Lebert and Lobo-Onell,[29] employed compensatory dialysis and concluded that all uric acid in the blood was free, as it was entirely dialyzable.

The question as to the colloidal and the bound state of uric acid in serum has not been settled by studies of uric acid clearance. Brøchner-Mortensen[31] expressed the belief that uric acid in the blood does not exist in a colloidal or combined form but that it is a true threshold substance, completely excreted by the glomeruli and probably partly reabsorbed by the tubules. Berglund and Frisk[32] however, assumed that part of the uric acid is in a nonfiltrable form, that only the free uric acid passes the kidney and that no reabsorption from the filtrate occurs.

Adlersberg, Grishman and Sobotka,[33] studied the partition of uric acid under normal and under pathologic conditions. The first series of experiments were performed with dialysis. Sera containing normal and elevated amounts of uric acid were dialyzed in cellophane bags. The uric acid was found to be completely dialyzable and the observation of Chabanier, Lebert and Lobo-Onell [29] could be confirmed. Essentially the same results were obtained in normal subjects after intravenous injection of uric acid which considerably raised the uric acid level of the serum. By subsequent exposure of these serum specimens to dialysis the uric acid was completely removed or traces of less than 0.04 mg. per hundred cubic centimeters remained. Apparently the equilibrium between free and combined uric acid is labile and can easily be disturbed by various factors, e.g., dialysis. Dialysis first removes the available free uric acid; this disturbs the equilibrium, and more uric acid is liberated, becomes dialyzable and is in turn removed from the serum. Hence, dialysis is not suitable for the study of uric acid partition in protein-containing fluids.

TABLE II—URIC ACID PARTITION IN NORMAL SUBJECTS AND IN PATIENTS WITH GOUT

	URIC ACID MG. PER 100CC. OF SERUM			
	Total uric acid	*Filtrable fraction*	*Non-filtrable fraction*	*Bound uric acid in % of total*
Normal Subjects	2.6—6.8 (5.0)*	2.2—5.8 (4.2)	0.2—1.3 (0.8)	4—24 (16)
Gout (10 pat.)	5.1—16.4 (9.2)	1.9—14.4 (7.4)	0.1—3.6 (1.8)	1—65 (20)

* Figures in parentheses are averages.

Satisfactory results were obtained by the use of ultrafiltration. The range of the total uric acid, the ultrafiltrable and the non-ultrafiltrable fractions was established by a series of determinations on normal subjects. The uric acid content of the serum varied from 2.6 to 6.8 mg. per hundred cubic centimeters. The ultrafiltrable fraction of the serum uric acid ranged from 2.2 to 5.8 mg. per hundred cubic centimeters, with an average of 4.2 mg. The nonfiltrable or bound uric acid ranged from 0.2 to 1.3 mg. per hundred cubic centimeters, with an average of 0.8 mg. Expressed in percentage of the total uric acid, the bound uric acid averaged 16 in normal subjects, with a range from 4 to 24 (see Table II).

The uric acid partition in patients with various pathologic conditions was subsequently examined. All important disease groups were included, such as pulmonary, cardiovascular, renal, and hepatic diseases; diseases of the blood, as well as conditions known to be associated with disturbance of purine metabolism, such as gout, uremia and forms of leukemia. It soon became evident that hepatic disease and gout may produce an anomalous picture. Normal values for total, as well as for bound, uric acid were encountered in acute cellulitis, typical allergic bronchial asthma, nephrotic hypoproteinemia, with total protein values varying from 3.4 to 5.2 Gm, per hundred cubic centimeters and with inversion of the albumin-globulin ratio, in diabetes with and without ketosis. Elevated values for total uric acid were associated with a normal partition in uremia with marked azotemia, in lymphatic leukemia, myeloid leukemia, myasthenia gravis and amyotrophic lateral sclerosis.

The serum uric acid partition in patients with exophthalmic goiter

was normal except in a patient, whose case history was published elsewhere, who suffered from a peculiar form of persistent hyperthyroidism or possibly a hypothalamic lesion, who exhibited active symptoms of the disease in association with unusual muscular disturbances.[33] In contrast, two other patients with exophthalmic goiter, before and during medication, showed a normal uric acid partition. Marked deviation from the normal figures both for total and for bound uric acid was observed in a man with multiple myeloma. The serum of this patient was of syrupy appearance and of abnormally high viscosity. The total protein content was 11.6 Gm. per hundred cubic centimeters, with 3.2 Gm. of albumin and 8.4 Gm. of globulin. The total uric acid content was 8.6 to 9.8 mg. per hundred cubic centimeters, the bound uric acid ratio, on two occasions, 36 and 37 per cent, respectively. A second patient with this disease but without hyperproteinemia displayed a normal uric acid picture. With the exception of the two patients with atypical exophthalmic goiter and with multiple myeloma, the uric acid partition, in the pathologic conditions studied, did not deviate from that of normal persons.

Changes in uric acid metabolism have frequently been reported in patients with hepatic disease.[34,35,36] In our own series,[33] a low titer of uric acid in the blood was met with only in patients with icterus of long duration and possible secondary hepatic damage (carcinoma of the pancreas, cholangitis with pylephlebitis). Patients with hepatitis and cirrhosis of the liver presented no consistent change in the total uric acid content of the blood, although in some instances they exhibited alterations of uric acid partition mostly in association with exacerbation of the disease. A group of patients with cirrhosis of the liver showed in the course of their illness normal figures changing into abnormal ones or vice versa. Thus, the value of 27 per cent bound uric acid in one patient decreased to 7 per cent within one week; the change was accompanied by clinical improvement. In contrast, another patient with cirrhosis of the liver started with a normal uric acid partition, and then, during the progressive deterioration of his general condition, which eventually led to a fatal outcome, showed gradual elevation of the bound uric acid ratio. Similarly, in some instances of hepatitis, normal values for total uric acid were associated with abnormal uric acid partition (up to 41 per cent bound uric acid). At the height of the disease and impairment of hepatic function, a disturbance of uric acid partition

prevailel, while uric acid partition was normal at the onset and during recovery. However, the material studied did not permit definite conclusions as to the relation between hepatic function and uric acid partition.

Ten patients with typical gout were studied. The levels of total uric acid in the serum of these patients were markedly elevated and varied from 5.1 to 16.4 mg. per hundred cubic centimeters; the average for all patients was 9.2 mg. per hundred cubic centimeters, almost double the average value for total uric acid in the serum of normal persons. The high level of the total uric acid was associated with an elevation of the free uric acid to 14.4 mg. per hundred cubic centimeters, with an average of 7.4 mg. The bound uric acid ranged between 0.1 and 3.6 mg. per hundred cubic centimeters, with an average of 1.8 mg., which was double the average bound uric acid in normal persons (see Table II).

Several observations of patients with gout will be briefly cited to illustrate the correlation of the findings with the clinical course. One patient had considerably elevated total uric acid levels (10.0 to 11.6 mg. per hundred cubic centimeters); the uric acid partition was fairly constant, the bound uric acid was 12 to 17 per cent of the total uric acid. Only on one occasion, during an attack of gout, was there an elevation of the bound uric acid to 24 per cent of the total uric acid. On initiation of colchicine therapy the symptoms promptly subsided, and two days later and thereafter the uric acid partition was normal. The elevation of the "bound" level simultaneously with the attack was of interest, although the value of 24 per cent bound uric acid falls just within the upper limit of normal. Similar elevations of the bound uric acid fraction were observed in other gouty individuals prior to or in early stages of an acute attack. A correlation of this phenomenon with the well known preparoxysmal diminished excretion of urinary uric acid might be considered.

Another patient with gout was never completely free of symptoms during the period of observation. Although the total uric acid content of the serum was high normal (5.5 to 5.8 mg. per hundred cubic centimeters), the uric acid partition was abnormal (26 to 65 per cent of bound uric acid). It is noteworthy that in this patient with typical gout a normal total uric acid content was associated throughout the period of observation with an abnormal uric acid partition. Another patient presented a similar picture, normal values for the total uric content (4.1 to 6 mg.

per hundred cubic centimeters), but an abnormal bound uric acid ratio of 27 to 33 per cent. On the other hand, hyperuricemia, even of an extremely high degree (13.0 and 16.4 mg. per hundred cubic centimeters), was associated in two patients with a normal uric acid partition (18 and 12 per cent, respectively) during the symptom-free period.

In several observations, colchicine resulted in lowering of the bound uric acid fraction without altering the total uric acid content. We surmised that the therapeutic effect of this drug in gout may be in some way connected with the "liberation" of uric acid in the blood and in the tissues.

The observations may be summarized as follows: Comparatively constant uric acid partition of the blood serum is characteristic of the normal individual. In pathologic conditions, gout and hepatic damage bring about disturbance of the uric acid partition, characterized by a diminution of the free, and elevation of the protein-bound, uric acid fraction. The liver is known to play an important role in protein as well as in purine metabolism; hence, hepatic disease may result in disturbances of this metabolic domain. In gout, the abnormal fixation of uric acid in blood and tissues might explain the retention and diminished elimination of this substance by the kidney.

The results of our studies on uric acid partition were confirmed and extended in observations by Wolfson, Levine, Tinsley and Huddlestun.[15-18] These authors analyzed the "total uric acid" of the plasma as well as the "true uric acid" (the amount of uric acid destroyed by uricase). The difference between total and true uric acid was attributed to chromogenic substances similar to those giving the color reaction for uric acid in plasma. Seventy-nine per cent of the plasma total urate and 77 per cent of the plasma true urate proved to be ultrafiltrable. In other words, 21 per cent and 23 per cent of the plasma urate, respectively, was bound urate, bound to plasma proteins. On the basis of these results and additional studies of uric acid clearance in man, Wolfson et al assume that the major portion of the plasma urate circulates in the form of polymeric urate complexes. Studies in normal and azotemic chickens added support to this hypothesis. However, it must be recalled that in birds uric acid is the chief end product of protein metabolism, analogous to urea in mammals, and therefore extreme caution is indicated in transfering these results to man. This conservative attitude is fully observed by Wolfson et al.

Hereditary Hyperuricemia: Its Relationship to a Hereditary Disturbance of Lipid Metarolism (Hereditary Hypercholesterolemia)

There is increasing interest among clinicians in human genetics and in the early detection of carriers of hereditary disease. Talbott[37] observed hyperuricemia in 25 per cent of the relatives of patients suffering from gout. Stecher and Hersh[38a] studied a group of thirty families, parents, siblings and offspring of gouty individuals. On the basis of numerical tests, they determined the mode of inheritance, the gene frequency, and penetrance. Smyth, Cotterman and Freyberg[38b] studied 87 relatives of 19 gouty male patients. Hyperuricemia in these families was apparently due to a single autosomal dominant gene, but only a fraction of the heterozygotes for this factor developed manifestations of gouty arthritis. Sex and age were also important factors determining the level of serum urate (see also, Smyth, Stecher and Wolfson[38c]). "The gene for essential hyperuricemia must be considered more common than one might suspect from the incidence of clinical gout."

We were particularly interested in these studies because of the relationship that apparently exists between hereditary hyperuricemia and hereditary hypercholesterolemia. In previous publications[39a, b, c] attention was called to the fact that familial xanthomatosis is not a rare disorder. It has long been so regarded because its two most striking external manifestations, xanthoma tuberosum and xanthoma tendinosum are met with infrequently. In a study[39b] of 35 xanthoma families comprising 172 members and an additional 29 individuals belonging to such families (total 201 persons), only 49 (24 per cent) exhibited the full syndrome, i.e., hypercholesterolemia, coronary artery disease and either xanthoma tuberosum or tendinosum or xanthelasma or corneal arcus. Elevation of serum cholesterol (to 300 mg. per cent or more) was found in 69 per cent of the examined individuals, coronary artery disease in 40 per cent. Xanthelasma of lids was present in about 30 per cent. Tuberous or tendinous xanthoma was present in only 12 per cent and all of these individuals had hypercholesterolemia excepting two whose cholesterol was unknown. Thus, the two most frequent abnormalities encountered among members of xanthoma families were hypercholesterolemia and coronary atherosclerosis; xanthelasma of the lids and corneal arcus were next in frequency, while xanthoma of skin or ten-

dons was least often found. Genetic analysis of the families supported the concept that the involved disturbance of cholesterol metabolism is inherited as an "incomplete" dominant trait.[39b]

The results obtained in the study of xanthoma families were compared with those of 122 unselected patients with proved coronary artery disease under age of 50 of whom seventy-one (58 per cent) had hypercholesterolemia.[39c] Fifty families of these patients were available for study. In fifteen families, all or most siblings exhibited hypercholesterolemia (300 mg. per cent or more) and in nine families one-half of the siblings showed this disturbance of cholesterol metabolism. Many siblings also exhibited xanthelasma and corneal arcus and a few xanthoma. Genetic analysis of these sibships by Stecher and Hersh[40] revealed that the number of individuals with hypercholesterolemia fitted a 1:1 Mendelian ratio and that hereditary transmission probably took place as a dominant trait.

Consideration of all data[39a, b, c] led to the concept that the common factor for younger individuals with coronary atherosclerosis may be a hereditary error of cholesterol metabolism. Familial xanthomatosis is then the most severe form of the inborn metabolic disturbance. Xanthoma lesions develop only in patients who carry two abnormal genes for cholesterol, i.e., are homozygotes. Atherosclerosis is frequent in such individuals. Many patients with uncomplicated coronary artery disease are probably affected with a milder form of disturbed lipid metabolism. They carry one abnormal gene for cholesterol, i.e., are heterozygotes. Derangement of cholesterol metabolism may help to explain the familial incidence of coronary artery disease and may also account in part for its development in many persons under 50 years of age.

Hypercholesterolemia may prove to be an inborn error of metabolism similar to gout, albinism or cystinuria, which are definitely dependent upon genetic factors.[40, 41] Since hereditary hyperuricemia and hereditary hypercholesterolemia apparently represent somewhat similar inborn errors of metabolism, it seemed profitable to study members of families exhibiting hereditary hypercholesterolemia for evidence of hyperuricemia. Actually, simultaneous occurrence and overlapping of both metabolic abnormalities was a not infrequent occurrence. Approximately one-third of our original patients showed both hypercholesterolemia and hyperuricemia.[39a] Since then, we have observed a number

of additional individuals, who showed both abnormalities without any evidence of clinical gout or renal disease.

Table III presents the data of 27 individual members of hypercholesterolemic families, whose serum cholesterol ranged from 250 to 870 mg. per one hundred cubic centimeters, average 452 mg. The uric acid concentration of the serum ranged from 2.5 to 9.4 mg. per one hundred cubic centimeters. A breakdown of these figures reveals that one-third of these persons exhibited hyperuricemia (levels above 6 mg. per one hundred cubic centimeters, range 6 to 9.4 mg.), one-third had borderline levels of 5 to 6 mg., and the rest had less than 5 mg. Interestingly enough, there were no clinical manifestations of gout (gouty arthritis) in the individuals who exhibited hyperuricemia. Wolfson[42] confirmed these observations and termed the syndrome: "Non-gouty hyperuricemia associated with familial hypercholesterolemia."

The coincidence of the two metabolic errors concerning purines and lipids may prove of importance in future studies of the underlying mechanisms which as yet are completely obscure. It is established that diets high in lipids result in diminished elimination of uric acid even in normal individuals, [43] an important fact to be remembered in the planning of diets for patients with gout. Following injection of adrenocorticotropic hormone of the pituitary (ACTH) there is a marked decrease of esterified cholesterol in the adrenals and an increased urinary excretion of uric acid. These well-established observations suggest closely related endocrine regulatory mechanisms of the cholesterol and uric acid metabolism by the pituitary-adrenocortical system. The occurrence of hyperuricemia and hereditary hypercholesterolemia in the same individual adds a new link to the relationship that exists between the metabolism of purines and that of lipids. Studies of genetic patterns of hyperuricemia in these families are in progress. Furthermore, investigation of adrenal cortical hormones in both gout and hereditary hypercholesterolemia may help to establish the possible function of the adrenal cortex in these disorders.

Allergic Factors in Gout

The sudden onset of the acute attack in gout and the full restitutio ad integrum, at least in the early phases of the disease, resembles an anaphylactic or allergic phenomenon.[44-47] Experienced clinicians always attributed great importance to certain foods and beverages, especially

TABLE III—OCCURRENCE OF HYPERURICEMIA IN INDIVIDUALS WITH HEREDITARY HYPERCHOLESTEROLEMIA

Patient No.	*Name*	*Cholesterol in mg. per 100 cc. of serum*		*Uric acid mg. per 100 cc. of serum*	*Classification of uric acid level*
		Total	*Esterified*		
1	Sp.	556	352	4.6	normal
2	Fi.	600	325		
		415	265	7.1	high
3	Gr.	490	310	5.0	borderline
		615	450	6.8	high
4	Fl.	390	220	4.5	normal
5	Scha.	350	250	5.4	borderline
6	Mi.	250	180	4.6	normal
7	Kr.	640	—	2.9	normal
8	Pr.	340	250	6.6	high
9	We.	450	375	4.0	normal
10	Ho.	410	290	4.5	normal
11	R. We.	410	295	5.5	borderline
12	St.	270	183	7.3	high
		325			
13	Schw.	266	—	5.6	borderline
14	Ad.	388	300	4.5	normal
15	Gr.	320	240	4.8	normal
16	F. Sh.	715	—	5.0	borderline
17	T. Sh.	460	425	5.4	borderline
18	Mo.	470	—	5.5	borderline
19	Ke.	640	—	1.5	normal
20	B. Schi.	870	—	4.3	normal
21	H. Schi.	720	—	2.7	normal
22	M. Schi.	310	—	2.7	normal
		380	154	2.5	normal
23	M. Mi.	375	154	6.0	high
24	Wo.	?	—	8.9	high
25	D. Fi.	330	—	9.4	high
26	Th.	280	—	6.4	high
27	Sw.	535	355	5.4	borderline

certain sorts of alcoholic drinks, as incitant of gouty attacks, possibly on an allergic basis. Recently, Harkavy[48] reported observations on three patients in whom acute attacks of gout were precipitated by specific sensitizing foods, pollens and combinations of both. In addition to typical joint symptons, renal symptoms were observed in one patient as temporary urinary suppression and albuminuria, while in another an overdose of pollen was followed by simultaneous response in the nasal, pulmonary and articular structures. Harkavy interpreted all these manifestations as vascular tissue reactions precipitated by a similar allergic mechanism. Favorable symptomatic results observed after administration of epinephrine were explained on the same basis.

The allergic aspect of clinical manifestations of gout has certainly received additional support by these studies. The individual afflicted with gout may thus be considered as a potential allergic "whose joints constitute the major shock tissue." Therapeutic management in these cases must eliminate the offending food and may include pollen immunization. Careful avoidance of allergenic insults may prevent acute exacerbations and thus mitigate the course of the disease. Therapeutic trials with antihistaminic drugs are suggested.

Summary

Problems of uric acid partition in the blood serum with special reference to the protein bound fraction were discussed. Abnormal fixation of uric acid in the serum was found in some instances of gout and in hepatic disease.

The occurrence of hereditary hypercholesterolemia and hyperuricemia in the same individual was emphasized. The coincidence of the two errors of metabolism may prove of importance in future studies of the underlying mechanism of these disorders. The possible role of endocrine mechanisms was discussed.

The importance of allergic factors in precipitating gouty attacks was stressed and therapeutic measures suggested.

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